EXHIBIT D

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 1**	**Master File No. 2:12-MD-02327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

Table of Contents

PROLIFT AND PROLIFT +M EXPERT OPINION

Ralph Zipper, MD FACOG, FPMRS

MEDICAL TRAINING BACKGROUND AND QUALIFICATIONS

I am board certified in Female Pelvic Medicine and Reconstructive Surgery (FPMRS) and Obstetrics/Gynecology. I received my medical degree in 1992 from The Mount Sinai School of Medicine of the City University of New York. In 1996, I completed my fellowship in the field of Obstetrics/Gynecology at the John Hopkins Hospital, Department of Gynecology and Obstetrics, Baltimore, Maryland. My practice of medicine has been dedicated to Urogynecology, FPMRS, for eighteen years. I am the president and director of Zipper Urogynecology Associates (ZUA), one of the busiest and most comprehensive private practice tertiary FPMRS referral centers in the U.S. Each year our team evaluates and treats over two thousand new patients. Over the last ten years, I have trained over one thousand urologists and gynecologists in the techniques of prolapse and incontinence surgery.

Over the last eighteen years, I have performed over one thousand mesh and biologic tissue implantations, pelvic organ prolapse procedures, and a similar number of native tissue prolapse surgeries. I have experience implanting most major mesh kits and self-tailored mesh and biologic grafts.

In addition to my role as a urogynecologist at ZUA, I am also currently serving as the President of Zipper Urogynecology Associates, the CEO of Uroshape, LLC (Develops laser technology for FPMRS), the President and COO of a Radio Frequency Surgical device company, the President of Afterglow, LLC (Develops FMPRS technology for Sexual Dysfunction and Pelvic Pain), and the CEO of Zipper Brothers Films, LLC (Documentary Film Company and Academy Award Winner). I am also actively providing C-level consulting services to a publically traded monoclonal antibody Pharma company. I have authored fifteen relevant patent applications and have been issued multiple patents relevant to the field of pelvic reconstructive surgery, which are published by the United States Patent and Trade Office. (Table 1)

Relevant to this litigation, between the years of 1998 and 2008, I served as the Keynote Speaker on Pelvic Reconstruction Surgery at the annual National Sales Meeting for both C.R. Bard and American Medical Systems. I was also hired to lecture physicians at national meetings on prolapse and incontinence surgery by both C.R. Bard and Coloplast. Additionally, Coloplast commissioned me and Dr. Neeraj Kohli to write an abstract on the NovaSilk mesh product. This was presented at IGUA in or about 2008. Additionally, I served as a product development consultant to Boston

Scientific. I met with Coloplast engineers and patent council to discuss my use of novel methods and devices for the treatment of stress urinary incontinence and pelvic organ prolapse. During this period of time, Coloplast paid to hold me in a "no-shop" agreement. I also served as a physician trainer for C.R. Bard for many years. During these years, over three hundred physicians from across the United States were sent by C.R. to watch me use the C.R. Bard prolapse and incontinence products. During this time, C.R. Bard also sought my opinion on product development, including the licensing and or purchasing of mesh products from inventors and manufacturers.

As a private independent consultant, I have worked closely with engineers to develop devices, including slings, for the treatment of stress urinary incontinence, methods for the treatment of stress urinary incontinence, and mesh products and methods for the treatment of pelvic organ prolapse, many of which were subsequently deployed and sold by foreign and U.S. medical device companies. In this same role, I worked extensively to develop instructional materials and marketing materials for prolapse mesh and incontinence products. Over one thousand hours were spent in these endeavors that resulted in commercialization.

As the president and Chief Operating Officer of a Bipolar Radio Frequency medical device company with an existing market clearance, some of my responsibilities include supervision and vetting of ongoing regulatory initiatives, development and supervision of ongoing labeling, supply chain, contract manufacturing, supervision of conformity attainment, supervision of all phases of R&D, including engineering, bench and animal testing, and clinical trials, and KOL contracting. As President of Uroshape LLC, I have many similar responsibilities.

I am familiar with the type of information that should be communicated to surgeons so that surgeons can make reasonable informed choices when considering medical products. I have read and am familiar with the Instructions for Use ("IFU"), sales and marketing materials, and physician training materials prepared by Ethicon for its pelvic floor and incontinence products. I have also reviewed the labeling for a multitude of pelvic floor products and incontinence products marketed by other companies, including the labels of products I have and have not implanted in my practice of FPMRS.

A current copy of my Curriculum Vita is attached as Exhibit "A". A current copy of my Fee Schedule is attached as Exhibit "B". A list of my court testimony and depositions is attached as Exhibit "C", as well as my fee schedule. In addition to my medical training, background and experience, the documents and materials I relied upon for this report are contained in Exhibit "D". Additionally, I relied upon those materials cited in this report and cited herein.

THE SURGICAL TREATMENT OF PELVIC ORGAN PROLAPSE

A hernia is a weakness in a body wall that allows internal organs to protrude. Hernias of the walls of the vagina are referred to as pelvic organ prolapse (POP). Where as few as 2% of all women will develop an abdominal wall hernia, as many as 50% of parous women will develop POP. Approximately 80% of women are asymptomatic to their POP with an estimated 19% lifetime risk of prolapse surgery.[1]

PELVIC ORGAN PROLAPSE SURGERIES

The goal of any prolapse surgery is to effectively treat a patient's symptoms. Typical symptoms of pelvic organ prolapse, as described in the International Urogynecology Association and International Continence Society joint report on the terminology for female pelvic floor dysfunction, are vaginal bulging (complaint of a bulge), pelvic pressure, bleeding, discharge, and infection (related to ulceration of the prolapse), splinting or digitation (applying pressure to the vagina, perineum or rectum to urinate or defecate), and low back ache.[2] Although not included in this standardized language, most experts recognize that the sexual experience can be negatively impacted by the awareness of prolapse and the sensation associated with the movement of prolapse during coitus. Significant pain with intercourse, also called dyspareunia, is not associated with prolapse and hence absent from the standardized language used by specialists when describing prolapse symptoms. However, patients with POP may have other disorders to past surgeries as a cause for dyspareunia.

Although the goal of POP surgery is to effectively treat symptoms, the historical weight of medical literature has utilized anatomic change, rather than symptomatic improvement, as a measure of success. As early as 2000, investigators realized the error of such metrics. Weber, et al., noted in their 2000 prospective study of native tissue surgery, that the majority of patients deemed failures secondary to anatomic endpoints were symptomatically cured and many had no visible prolapse. In 2011, these same authors reanalyzed their data, focusing on symptomatic improvement and the absence of visible prolapse; 89% of patients remained successfully treated and 100% had symptomatic improvement. A more recent publication on PROLIFT utilized a similar anatomic endpoint to define success.[3] Other authors, including those who have performed systematic reviews of the prolapse literature, have drawn similar conclusions. In 2007, in their systematic review of the literature, Morgan, et al.

---

[1] Surgical management of pelvic organ prolapse in women (Review). Copyright @ 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. Smith, Fiona J., C. D'arcy J. Holman, Rachael E. Moorin, and Nicolas Tsokos. "Lifetime Risk of Undergoing Surgery for Pelvic Organ Prolapse." Obstetrics & Gynecology. 116.5 (2010): 1096-100. Digesu, G. Alessandro, Charlotte Chaliha, Stefano Salvatore, Anna Hutchings, and Vik Khullar. "The Relationship of Vaginal Prolapse Severity Tosymptoms and Quality of Life." BJOG: An International Journal of Obstetrics and Gynaecology 112.7 (2005): 971-76.

[2] Haylen, Bernard, Dirk De Ridder, Robert Freeman, Steven Swift, Bary Berghmans, Joseph Lee, Ash Monga, Eckhard Petri, Diaa Rizk, Peter Sand, and Gabriel Schaer. "An International Urogynecological Association (IUGA)/International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Floor Dysfunction." Textbook of Female Urology and Urogynecology, Third Edition (2010): 1090-105.

[3] Weber M. Anne, Walters M. D., Piedmonte MA. Et al. Anterior Colporrhaphy: A randomized trial of three surgical techniques. Am J Obstet Gynecol. 2001. Vol 185, 6, 1299-1306. Chmielewski L, Walters MD, Weber AM, et al. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol 2011;205:69.e1-8. Jacquetin, B., P. Hinoul, J. Gauld, B. Fatton, C. Rosenthal, H. Clavé, O. Garbin, J. Berrocal, R. Villet, D. Salet-Lizée, P. Debodinance, and M. Cosson. "Total Transvaginal Mesh (TVM) Technique for Treatment of Pelvic Organ Prolapse: A 5-year Prospective Follow-up Study." .International Urogynecology Journal Int Urogynecology 24.10 (2013): 1679-686.

concluded, "The current recommendations (defining success by stringent anatomic end points) therefore label many individuals who are satisfied with their outcomes as failures. This could encourage surgeons to strive for an anatomic result that does not apparently make a difference for patients in terms of relief of prolapse symptoms."[4]

The surgical correction of pelvic organ prolapse has been well documented since the early 1900s. The principles of such traditional surgical correction are simple. The surgeon uses suture material to mend the patient's herniated native tissue. When the uterus is prolapsed, a hysterectomy may also be performed. These surgeries and the associated anatomy have been and continue to be extensively trained in both general obstetrical and urologic residency programs. These traditional surgeries, often called native tissue surgery, may be performed without the use of any novel medical devices.

The Traditional (Native Tissue) Prolapse Surgeries:

Colporrhaphies: This group of surgeries involves the suturing together of defects of the anterior wall of the vagina (the wall that supports the bladder), and or the posterior wall of the vagina (the wall that separates the rectum from the bladder). When performed on the anterior wall, the surgery is called an anterior colporrhaphy. When performed on the posterior wall, the surgery is called a posterior colporrhaphy. A variation of the anterior colporrhaphy is called the paravaginal repair. This surgery repairs a lateral defect of the anterior vaginal wall by suturing it to a thickening of tissue called the arcus tendineous fascia pelvis (ATFP).

> **Success:** As these surgeries have been performed for over a century, the overwhelming majority of reports on efficacy pre-date the more recent focus on subjective improvement (rather than anatomic measurements). Success rates based upon more stringent anatomic criteria, rather than the more recent criteria focusing on symptoms and awareness of POP, range from 30% to 65%, while success rates focusing on anatomic cure above the hymenal ring and symptomatic improvement have demonstrated 89% and 100% improvement.[5]
>
> **Complications:** Pain with intercourse has been reported to occur following 2-9% of colporrhaphies and is most typically associated with an optional component of posterior colporrhaphy, in which the muscles are sutured together (levator plication).[6] De novo stress urinary incontinence may occur in

[4] Morgan, Daniel M., Mary A. M. Rogers, Markus Huebner, John T. Wei, and John O. Delancey. "Heterogeneity in Anatomic Outcome of Sacrospinous Ligament Fixation for Prolapse." Obstetrics & Gynecology 109.6 (2007): 1424-433.

[5] Chmielewski L, Walters MD, Weber AM, Barber MD. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecology 2011;205:69.e1–69.e8 (mean f/u approx 2 years)

[6] Fatton B, Lagrange E, Jacquetin B. Sexual Outcome After Transvaginal Repair Of Pelvic Organ Prolapse (Pop) With And Without Mesh: A Prospective Study Of 323 Patients. ICS Abstract. Weber, Anne M., Mark D. Walters, Marion R. Piedmonte, and Lester A. Ballard. "Anterior Colporrhaphy: A Randomized Trial of Three Surgical Techniques." .American Journal of Obstetrics and Gynecology 185.6 (2001): 1299-306. Karram, Mickey, and Christopher Maher. "Surgery for Posterior Vaginal Wall Prolapse." International Urogynecology Journal Int Urogynecology 24.11 (2013): 1835-841. Weber, Anne M., Mark D. Walters, and Marion R. Piedmonte. "Sexual Function and Vaginal Anatomy in Women before and after Surgery for Pelvic Organ Prolapse and Urinary Incontinence." American Journal of Obstetrics and Gynecology 182.6 (2000): 1610-615. (corrected for complaints unrelated to colporrhaphy).

up to 6% of women undergoing anterior colporrhaphy. Prolapse of the untreated posterior compartment may follow 10% of anterior colporrhaphies.[7] Hemorrhage and infection occur in less than one percent of cases. Complications with native tissue surgeries are rarely significant, typically transient, and rarely require surgical intervention.

Vaginal Colpopexies: This group of surgeries involves the suspension of the vaginal apex. This is also referred to as the creation of level one support. Surgeons performing these surgeries utilize suture material to attach the vagina and its surrounding fascia (pubovaginal fascia and or paracervical ring) to dense ligaments of the pelvis (Sacrospinous Ligaments or Uterosacral Ligaments).

Success: A systematic review of Sacropinous Colpopexy in studies demonstrates a 95-97% success rate (one included study utilized the more stringent POP-Q anatomic definition of failure, stage 2 or greater, and reported a 95% success rate).[8] A recent randomized controlled trial reported a 2 year 94% success rate (apex above the hymenal ring)[9]. That same study found a 94% success rate of Uterosacral colpopexy. Repeat surgery was only 5% (majority not for apical failure).

Complications: Uterosacral Colpopexy is associated with a 0-1% incidence of ureteral injury (although intraoperative identification of kinking with intraoperative correction may be higher).[10] Dyspareunia is an uncommon event following uterosacral colpopexy and remains a reportable event. Sacrospinous Colpopexy is associated with a 6-14% incidence of transient buttock and or leg pain that almost always resolves within 6-12 weeks.[11]

Abdominal Colpopexies: Vaginal vault suspensions may be performed abdominally. These surgeries may be performed through a traditional incision (laparotomy) or by laparoscopy (Traditional or with the assistance of the da Vinci Robot). Uterosacral

---

[7] Vollebregt A, Fischer K, Gietelink D, van der Vaart C. Primary surgical repair of anterior vaginal prolapse: a randomized trial comparing anatomical and functional outcome between anterior colporrhaphy and trocar-guided transobturator anterior mesh. BJOG 2011;118:1518–1527

[8] Morgan, Daniel M., Mary A. M. Rogers, Markus Huebner, John T. Wei, and John O. Delancey. "Heterogeneity in Anatomic Outcome of Sacrospinous Ligament Fixation for Prolapse." Obstetrics & Gynecology 109.6 (2007): 1424-433. (mean f/u approx 2 yrs)

[9] Barber, Matthew D., Linda Brubaker, Kathryn L. Burgio, Holly E. Richter, Ingrid Nygaard, Alison C. Weidner, Shawn A. Menefee, Emily S. Lukacz, Peggy Norton, Joseph Schaffer, John N. Nguyen, Diane Borello-France, Patricia S. Goode, Sharon Jakus-Waldman, Cathie Spino, Lauren Klein Warren, Marie G. Gantz, and Susan F. Meikle. "Comparison of 2 Transvaginal Surgical Approaches and Perioperative Behavioral Therapy for Apical Vaginal Prolapse." Obstetrical & Gynecological Survey 69.7 (2014): 393-95.

[10] Diwadkar, Gouri B., Matthew D. Barber, Benjamin Feiner, Christopher Maher, and J. Eric Jelovsek. "Complication and Reoperation Rates After Apical Vaginal Prolapse Surgical Repair." .Obstetrics & Gynecology 113.2, Part 1 (2009): 367-73. Barber, Matthew D., Linda Brubaker, Kathryn L. Burgio, Holly E. Richter, Ingrid Nygaard, Alison C. Weidner, Shawn A. Menefee, Emily S. Lukacz, Peggy Norton, Joseph Schaffer, John N. Nguyen, Diane Borello-France, Patricia S. Goode, Sharon Jakus-Waldman, Cathie Spino, Lauren Klein Warren, Marie G. Gantz, and Susan F. Meikle. "Comparison of 2 Transvaginal Surgical Approaches and Perioperative Behavioral Therapy for Apical Vaginal Prolapse." Jama 311.10 (2014): 1023.

[11] Dietz, Viviane et al. "Functional Outcome after Sacrospinous Hysteropexy for Uterine Descensus." International Urogynecology Journal and Pelvic Floor Dysfunction 19.6 (2008): 747–752. PMC. Web. 15 Dec. 2015.

colpopexy may be performed abdominally and such is associated with slightly higher success rates (and lower ureteral injury rates) than when performed vaginally.[12] However, the most efficacious of all colpopexies remains the Abdominal Sacrocolpopexy.

Abdominal Sacrocolpopexy involves the suspension of the vagina to a ligament overlying the sacral promontory. This colpopexy is distinct from other colpopexies in two ways. The suspension is typically performed with a piece of synthetic mesh that overlays the vagina and is secured to the longitudinal ligament overlying the sacrum. Additionally, the vagina is not suspended to a ligament that is inside the pelvis. It is suspended to a ligament overlying the sacral promontory. Hence, there is no fixation to or through any muscles of the pelvis or encroachment upon the rectum. Hence, material defects of polypropylene mesh resulting in inflammation and contraction have minimal consequences in comparison to procedures that attach mesh to or pull mesh through muscles of the pelvis (discussed later in this monograph).

> **Success:** Systematic and comprehensive reviews of the literature demonstrate a success rate of abdominal Sacrocolpopexy ranging from 93-97% months.[13] Laparoscopic Sacrocolpopexy (the same surgery performed laparoscopically with or without the da Vinci Robot) is associated with a similar success rate.[14]
>
> **Complications:** The overwhelming majority of studies demonstrate a 0-10% incidence of post-operative de novo dyspareunia with studies in the higher range being typically confounded by concomitant surgery.[15] Mesh exposure following abdominal hysterectomy occurs following approximately 4% of cases with higher rates being limited to those cases with concomitant hysterectomy.[16] Laparoscopic Sacrocolpopexy (with or without the da Vinci Robot) is associated with a similar or lower incidence of mesh erosion.[17]

By the late 1990s, following the decades of mesh use by general surgeons in the treatment of abdominal hernias, some expert pelvic surgeons began to experiment with transvaginal mesh surgery in the treatment of POP. These surgeries were simple

---

[12] Rardin, Charles R. et al. "Uterosacral Colpopexy at the Time of Vaginal Hysterectomy: Comparison of Laparoscopic and Vaginal Approaches." The Journal of reproductive medicine 54.5 (2009): 273–280.

[13] Anne-Lotte W. M. Coolen, Anique M. J. van Oudheusden, Hugo W. F. van Eijndhoven, et al., "A Comparison of Complications between Open Abdominal Sacrocolpopexy and Laparoscopic Sacrocolpopexy for the Treatment of Vault Prolapse," Obstetrics and Gynecology International, vol. 2013, Article ID 528636, 7 pages, 2013. doi:10.1155/2013/528636

[14] Ganatra, Anjali M., François Rozet, Rafael Sanchez-Salas, Eric Barret, Marc Galiano, Xavier Cathelineau, and Guy Vallancien. "The Current Status of Laparoscopic Sacrocolpopexy: A Review." European Urology 55.5 (2009): 1089-105. Hudson, Catherine O. et al. "Outcomes of Robotic Sacrocolpopexy: A Systematic Review and Meta-Analysis." Female pelvic medicine & reconstructive surgery 20.5 (2014): 252–260. PMC. 15 Dec. 2015.

[15] Nygaard, Ingrid E., Rebecca Mccreery, Linda Brubaker, Annamarie Connolly, Geoff Cundiff, Anne M. Weber, and Halina Zyczynski. "Abdominal Sacrocolpopexy: A Comprehensive Review." Obstetrics & Gynecology 104.4 (2004): 805-23.

[16] Nygaard, Ingrid E., Rebecca Mccreery, Linda Brubaker, Annamarie Connolly, Geoff Cundiff, Anne M. Weber, and Halina Zyczynski. "Abdominal Sacrocolpopexy: A Comprehensive Review." Obstetrics & Gynecology 104.4 (2004): 805-23.

[17] Richard K. L., Alexandre Mottrie, Christopher K. Payne, David Waltregny. A Review of the Current Status of Laparoscopic and Robot-assisted Sacrocolpopexy for Pelvic Organ Prolapse. European Urology 65 (2014) 1128–1137

modifications of traditional colporrhaphies and involved neither novel anatomy, nor novel instrumentation. In or about 2005, Ethicon introduced to the U.S. market a novel One-Size-Fits-All mesh kit for the treatment of pelvic organ prolapse, PROLIFT. The PROLIFT mesh device was to be placed in a novel method using new instrumentation.

Transvaginal Mesh Implantation Surgeries:

Self-Tailored Mesh: The late 1990s marks the time when an elite group of expert urogynecologists began to gain experience with the transvaginal implantation of polypropylene mesh in the treatment of pelvic organ prolapse. These surgeons would cut pieces of mesh to match the anatomy of each individual patient and then attach the mesh to pelvic fascia or ligaments with suture material. Evidence of the marked variation in size and shape utilized by these surgeons is the GYNEMESH PS Device Validation data.[18] In this validation study, Ethicon recruited 6 Key Opinion Leader urogynecologists to test GYNEMESH PS and confirm that it conformed to the needs and intended uses. Each of these surgeons had extensive experience with self-tailored mesh implantation (80-250 surgeries). Four of the six surgeons performed a cystocele repair with no two surgeons cutting a similar size or shape (4 x 2.5, 6 x 7, 11 x 8, and 4 x 3 cm). Self-Tailored mesh implantation surgeries neither involved novel surgical instrumentation, nor novel surgical dissection. Surgeons were able to rely effectively on the learning of their residency programs. Very little was ever published with regard to the efficacy and complications associated with self-tailored transvaginal mesh implantation. There is no evidence to demonstrate equal or superior efficacy to native tissue surgery and mesh erosions were common. Visco, et al. had previously documented the risk of transvaginal mesh erosion in 2001. These authors performed a retrospective analysis that compared Abdominal Sacrocolpopexy to colpopexies that placed mesh transvaginally and found a 3.2% vs. 16% risk of erosion, respectively.[19]

One-Size-Fits-All Blind-Pass Armed Mesh Kits:

Coincident to the growing use of self-tailored transvaginal mesh implantation amongst expert pelvic surgeons, medical device companies introduced to the market a series of novel transvaginal mesh kits. The first of these kits, PROLIFT, was introduced by Ethicon in 2005. Whereas self-tailored mesh involved no novel instrumentation or method, the PROLIFT kit and other kits that followed introduced a novel surgical method for the transvaginal implantation of mesh in the treatment of pelvic organ prolapse. This novel method caused surgeons to traverse anatomy that was not trained in residency programs and, in addition, required novel instrumentation. Surgeons would no longer be able to create shapes to match their patient's unique anatomic dimensions. This kit (and others that followed) provided a one-size-fits-all

[18] ETH.02089268

[19] Visco, Anthony G., Alison C. Weidner, Matthew D. Barber, Evan R. Myers, Geoffrey W. Cundiff, Richard C. Bump, and W. Allen Addison. "Vaginal Mesh Erosion After Abdominal Sacral Colpopexy." .Obstetric and Gynecologic Survey</i> 56.7 (2001): 410-11.

mesh shape that allowed for only minor modifications. This mesh shape (and others that followed) included a central body segment and peripheral arms. Surgeons were instructed to use novel instruments to pull the mesh arms through muscles of the pelvic sidewalls and floor, blindly traversing unfamiliar anatomy. Systematic review of the literature fails to demonstrate evidence in support of such kits for the treatment of posterior vaginal wall prolapse or apical prolapse, demonstrates inferiority for apical prolapse, fails to demonstrate any quality of life advantage versus other methods of prolapse repair (any compartment), and demonstrates significantly higher complication rates. The use of such transvaginal mesh kits in the treatment of anterior pelvic organ prolapse may yield an improved POP-Q score (anatomic result), but has not been shown to offer any improved quality of life in exchange for the increased complications.[20]

Success: Prospective data on apical prolapse has shown Total PROLIFT to be associated with a 43-79% success rate.[21] Minimal data exist for efficacy of other mesh kits in the treatment of apical prolapse. Systematic review of armed mesh in the treatment of anterior prolapse demonstrates an 86% success rate. In at least two-thirds of the considered studies, a native tissue anterior repair was performed concomitantly. The 86% success rate is not corrected for the uniquely high incidence of de novo prolapse in the untreated compartment. This is reported to be as high as 53%.[22] Hence, the data provide an overall success rate of below 50%. Success of PROLIFT in the posterior compartment may be as high as 89%. However, with correction for the unique elevation of de novo untreated compartment failure, success may be as low as 55%.[23] In fact, the five year U.S. prospective study of the PROLIFT armed mesh demonstrated a 77% success rate in the treated compartment, but an overall success rate of 66% (including the de novo development of prolapse in the compartments not treated with mesh). This effect was noted at the time of the 3 year follow-up.[24]

Complications: The rate of de novo dyspareunia associated with PROLIFT is 10-26%.[25] The inventor of the PROLIFT method, investigator, and author in the

---

[20] Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD004014. DOI: 10.1002/14651858.CD004014.pub5

[21] Maher CF, Feiner B, Decuyper EM, Nichlos CJ, Hickey KV, O'Rourke P. Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: a randomized trial. American Journal of Obstetrics and Gynecology 2011;204(4):e361-7.

[22] Milani AL, Withagen MIJ, Vierhout ME. Outcomes and predictors of failure of trocar-guided vaginal mesh surgery for pelvic organ prolapse.. Am J Obstet Gynecol 2012;206:440.e1-8.

[23] Milani AL, Withagen MIJ, Vierhout ME. Outcomes and predictors of failure of trocar-guided vaginal mesh surgery for pelvic organ prolapse. Am J Obstet Gynecol 2012;206:440.e1-8.

[24] Miller, Dennis, Vincent Lucente, Elizabeth Babin, Patricia Beach, Peter Jones, and David Robinson. "Prospective Clinical Assessment of the Transvaginal Mesh Technique for Treatment of Pelvic Organ Prolapse-5-Year Results." Female Pelvic Medicine & Reconstructive Surgery 17.3 (2011): 139-43.

[25] Jacquetin, B., P. Hinoul, J. Gauld, B. Fatton, C. Rosenthal, H. Clavé, O. Garbin, J. Berrocal, R. Villet, D. Salet-Lizée, P. Debodinance, and M. Cosson. "Total Transvaginal Mesh (TVM) Technique for Treatment of Pelvic Organ Prolapse: A 5-year Prospective Follow-up Study." .International Urogynecology Journal Int Urogynecology 24.10 (2013): 1679-686. Fatton B, Lagrange E, Jacquetin B. Sexual Outcome After Transvaginal Repair Of Pelvic Organ Prolapse (Pop) With And Without Mesh: A Prospective Study Of 323 Patients. ICS Abstract. See Hammons v. Ethicon, Inc., et al. Deposition of Joye K. Lowman, M.D., M.P.H. taken on 11/13/15. Pgs

5 year PROLIFT study found the de novo dyspareunia rate of PROLIFT to be five times that of native tissue surgery. PROLIFT is also associated with a contraction of vaginal length (TVL). The initial study on the PROLIFT procedure demonstrated 12.6% of women to be with moderate to severe vaginal retraction.[26] Significant decreases in vaginal length as well as significant decreases in vaginal length in comparison to Sacrocolpopexy were demonstrated by Maher, et al. These investigators found no significant change from a mean pre-op TVL of 9 cm in the no mesh group, whereas the Total PROLIFT group had a decrease in TVL from 9 to 7.8 cm.[27] Mesh erosion into or through the vaginal mucosa (skin of the vagina) occurs in up to 23% of cases.[28] The investigators of the manufacturer-sponsored 5-year U.S. prospective trial on PROLIFT reported a 19% incidence of mesh erosion, with more than half of patients requiring surgical intervention and almost 40% having recurrent episodes of mesh extrusion.[29] Prospective data , randomized prospective trials, and systematic review of the literature have demonstrated that transvaginal mesh implantation is associated with a significantly higher incidence of de novo stress urinary incontinence than native tissue surgery, with a rate of de novo stress urinary incontinence following transvaginal polypropylene mesh implantation ranging from 12 to 36%.[30] Svabik, et al. found a 36% incidence of de novo stress urinary incontinence following PROLIFT, versus 9% with native tissue surgery.

The implantation of armed mesh is also associated, as already noted herein, with a unique increase in the risk of untreated compartment de novo pelvic organ prolapse. Shortly after the transvaginal implantation of armed mesh, 20-40% of women will develop pelvic organ prolapse in the compartment/s not covered by mesh.[31] This is 2-4 times greater than that expected for native

---

175-176. Marie¨lla I Withagen, M, et al. Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse. Amer Coll Obstet and Gyn 2011; 117:No2,Pt1;

[26] ETH.MESH.00012009

[27] Maher CF, Feiner B, Decuyper EM, Nichlos CJ, Hickey KV, O'Rourke P. Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: a randomized trial. American Journal of Obstetrics and Gynecology 2011;204(4):e361-7.

[28] Miller D., et al. Prospective Clinical Assessment of the Transvaginal Mesh Technique for Treatment of Pelvic Organ Prolapse - 5-Year Results. Female Pelvic Med Reconstr Surg 2011; 17: 139-143., Svabik K. Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial. Ultrasound Obstet Gynecol 2014; 1-7. DOI: 10.1002/uog.13305. Simone Dos Reis Brandão Da Silveira, Jorge Milhem Haddad, Zsuzsanna Ilona Katalin De Jármy-Di Bella, Fernanda Nastri, Miriam Goncalves Markos Kawabata, Silvia Da Silva Carramão, Claudinei Alves Rodrigues, Edmund Chada Baracat, and Antonio Pedro Flores Auge. "Multicenter, Randomized Trial Comparing Native Vaginal Tissue Repair and Synthetic Mesh Repair for Genital Prolapse Surgical Treatment." .International Urogynecology Journal Int Urogynecology 26.3 (2014): 335-42.

[29] [29] Miller D., et al. Prospective Clinical Assessment of the Transvaginal Mesh Technique for Treatment of Pelvic Organ Prolapse - 5-Year Results. Female Pelvic Med Reconstr Surg 2011; 17: 139-143

[30] Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD004014. DOI: 10.1002/14651858.CD004014.pub5. Svabik, K., A. Martan, J. Masata, R. El-Haddad, and P. Hubka. "Comparison of Vaginal Mesh Repair with Sacrospinous Vaginal Colpopexy in the Management of Vaginal Vault Prolapse after Hysterectomy in Patients with Levator Ani Avulsion: A Randomized Controlled Trial." Ultrasound Obstet Gynecol Ultrasound in Obstetrics & Gynecology 43.4 (2014): 365-71. Krcmar M, Krofta L, Feyereisl J1, Otcenasek M, Kasikova E, Dlouha K. Six Years Experience Of Using Mesh Implants In Pelvic Floor
Reconstructive Surgery. International Continence Society Abstract

[31] Withagen, M, et al. Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse. Amer Coll Obstet and Gyn 2011; 117:No2,Pt1; Vollebregt A, Fischer K, Gietelink D, van der Vaart C. Primary surgical repair of anterior vaginal

tissue prolapse surgery. In addition to the above noted complications, the use of armed mesh, with its associated novel instrumentation, introduced another unique complication not associated with traditional surgeries, extra-pelvic infections. [32] Although uncommon, these infections can be severe and difficult to treat. The excessive incidence of complications, as well as the introduction of novel complications, ultimately resulted in a re-operation rate that exceeded that of any other prolapse surgeries. Maher, et al. found that only 6% of Sacrocolpopexy patients required re-operation versus 22% of PROLIFT patients.[33] Other authors, including investigators from the French and U.S. 5 year prospective PROLIFT trial, have reported a re-operation rate of 15-21% (including extrusion procedures).[34] This uniquely high re-operation rate is in large part secondary to the high incidence of mesh erosion, untreated compartment failure, and the chronic and refractory nature of mesh related dyspareunia.

Comparison of Complications:

Although it is true that surgical complications such as dyspareunia, de novo stress urinary incontinence, and untreated compartment failure occur with both native tissue repairs and transvaginal polypropylene mesh implantation, as noted above, the incidence of such complications is significantly higher with mesh implantation. Beyond this concerning increase in known surgical complications, the transvaginal implantation of mesh introduces a high incidence of new and unique complications, complications not previously known to prolapse surgery, including erosion, extra-pelvic infection, and clinically significant vaginal contraction. However, of greatest concern is the fact that surgical complications of transvaginal mesh, as discussed elsewhere in this monograph, are much more difficult to treat than those same complications arising from a native tissue surgical repair. Some complications of armed transvaginal mesh implantation, such as dyspareunia, are often untreatable, resulting in life-long dyspareunia or apareunia.[35]

---

prolapse: a randomized trial comparing anatomical and functional outcome between anterior colporrhaphy and trocar-guided transobturator anterior mesh. BJOG 2011;118:1518–1527

[32] Zyczynski HM, Carey MP, Smith ARB, et al. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:587.e1-8.

[33] Maher CF, Feiner B, Decuyper EM, Nichlos CJ, Hickey KV, O'Rourke P. Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: a randomized trial. American Journal of Obstetrics and Gynecology 2011;204(4):e361-7

[34] Jacquetin, B., P. Hinoul, J. Gauld, B. Fatton, C. Rosenthal, H. Clavé, O. Garbin, J. Berrocal, R. Villet, D. Salet-Lizée, P. Debodinance, and M. Cosson. "Total Transvaginal Mesh (TVM) Technique for Treatment of Pelvic Organ Prolapse: A 5-year Prospective Follow-up Study." .International Urogynecology Journal Int Urogynecol J</i> 24.10 (2013): 1679-686. Miller D., et al. Prospective Clinical Assessment of the Transvaginal Mesh Technique for Treatment of Pelvic Organ Prolapse - 5-Year Results. Female Pelvic Med Reconstr Surg 2011; 17: 139-143. The cited reoperation rate includes procedures for extrusions.

[35] Crosby, Erin C., Melinda Abernethy, Mitchell B. Berger, John O. Delancey, Dee E. Fenner, and Daniel M. Morgan. "Symptom Resolution After Operative Management of Complications From Transvaginal Mesh." .Obstetrics & Gynecology. 123.1 (2014): 134-39. Abot S,Unger C A, Evans J M, etal.Evaluation and management of complications from synthetic mesh after pelvic reconstructive surgery: a multicenter study.Am J Obstet Gynecol 2014;210:163.eí-8. Blandon, Roberta E., John B. Gebhart, Emanuel C. Trabuco, and Christopher J. Klingele. "Complications from Vaginally Placed Mesh in Pelvic Reconstructive Surgery." .International Urogynecology Journal Int Urogynecol J.20.5 (2009): 523-31.

Systematic reviews of the literature, representing the highest level of medical evidence, have failed to demonstrate any superiority of transvaginal mesh in the treatment of POP symptoms. Although there exists some evidence that transvaginal mesh may improve anatomic success and the symptom of bulge in the anterior compartment, there is still no evidence to demonstrate that mesh surgery has a quality of life benefit in any area of the vagina. In stark contrast to the lack of evidence to support the transvaginal implantation of mesh, the systematic reviews and prospective level one data have repeatedly demonstrated, in comparison to native tissue surgery, a significant and concerning increase in complications and the event of new, difficult to treat, and often untreatable complications. These concerns were validated by the FDA in both its 2008 Public Health Notice (PHN) and its 2011 Safety Communication, by the American College of Obstetrics and Gynecology and the American Urogynecology Society, and the American Urologic Society.

2008 FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence.[36]

- *The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence.*
- *In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia.*
- *Inform patients that implantation of surgical mesh is permanent, and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication.*
- *Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall (in POP repair).*

2011 UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse: FDA Safety Communication.[37]

- *The FDA is issuing this update to inform you that serious complications associated with surgical mesh for transvaginal repair of POP are not rare.*
- *Furthermore, it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair in all patients with POP and it may expose patients to greater risk.*
- *Mesh used in transvaginal POP repair introduces risks not present in traditional non-mesh surgery for POP repair.*

---

[36] FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence. Issued: October 20, 2008

[37] FDA Safety Communication. UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse: FDA Safety Communication. Date Issued: July 13, 2011

- *There is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh.*
- *The FDA's literature review found that erosion of mesh through the vagina is the most common and consistently reported mesh-related complication from transvaginal POP surgeries using mesh. Mesh erosion can require multiple surgeries to repair and can be debilitating for some women. In some cases, even multiple surgeries will not resolve the complication.*
- *Reports in the literature associate mesh contraction with vaginal shortening, vaginal tightening and vaginal pain.*
- *Both mesh erosion and mesh contraction may lead to severe pelvic pain, painful sexual intercourse or an inability to engage in sexual intercourse. Also, men may experience irritation and pain to the penis during sexual intercourse when the mesh is exposed in mesh erosion.*
- *Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall in POP repair using surgical mesh.*
- *Recognize that in most cases, POP can be treated successfully without mesh thus avoiding the risk of mesh-related complications.*
- *Removal of mesh due to mesh complications may involve multiple surgeries and significantly impair the patient's quality of life. Complete removal of mesh may not be possible and may not result in complete resolution of complications, including pain.*
- *Ensure that the patient understands the postoperative risks and complications of mesh surgery as well as limited long-term outcomes data.*

2011 American College of Obstetrics and Gynecologists and American Urogynecology Society Committee Opinion. Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse.[38]

- *Mesh kits for repair of POP were first marketed to urologists and gynecologists as a way to improve success rates for POP repairs with native tissue, but without well- designed trials to establish the safety and efficacy of these devices.*
- *With the use of a composite of anatomic success, patient-oriented improvement and satisfaction, and total reoperation rates, success rates of native tissue repairs may be higher than previously thought*
    - *The risk/benefit ratio for mesh-augmented vaginal repairs must balance improved anatomic support of the anterior vaginal wall against the cost of the devices and increased complications such as mesh erosion, exposure, or extrusion; pelvic pain; groin pain; and dyspareunia.*

[38] The American College of Obstetricians and Gynecologists. Committee Opinion. Committee on Gynecologic Practice. Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse. Number 513. December 2011.

- *Surgeons performing complex pelvic floor reconstructive surgery should have adequate experience and training in native tissue repairs as well as repairs using mesh augmentation specific to each device, should have a thorough understanding of pelvic anatomy, and should be able to counsel patients regarding the risk/benefit ratio on the use of mesh compared with native tissue repairs.*
- *Compared with existing mesh products and devices, new products should not be assumed to have equal or improved safety and efficacy unless clinical long-term data are available.*

2011 American Urologic Society Position Statement on The Use of Vaginal Mesh for the Repair of Pelvic Organ Prolapse.[39]

- *The AUA strongly agrees with the FDA that a thorough informed consent should be conducted prior to the use of mesh products for pelvic organ prolapse. The AUA also agrees with the FDA statement that surgeons who wish to utilize mesh techniques for pelvic organ prolapse should:*
  - *Undergo rigorous training in the principles of pelvic anatomy and pelvic surgery.*
  - *Be properly trained in specific mesh implantation techniques.*
  - *Be able to recognize and manage complications associated with vaginal mesh*

2011 Society of Obstetricians and Gynaecologists of Canada Technical Update. Transvaginal Mesh Procedures for Pelvic Organ Prolapse.[40]

- *Patients should undergo thorough preoperative counseling regarding (a) the potential serious adverse sequelae of transvaginal mesh repairs, including mesh exposure, pain, and dyspareunia; and (b) the limited data available comparing transvaginal mesh systems with traditional vaginal prolapse repairs or with traditional use of graft material in the form of augmented colporrhaphy and sacral colpopexy.*
- *Until appropriate supportive data are available, new trocarless kits should be considered investigative.*

---

[39] American Urologic Association. AUA Position Statement On The Use Of Vaginal Mesh For The Repair Of Pelvic Organ Prolapse. Board of Directors, November 2011. https://www.auanet.org/education/vaginal-mesh-for-pelvic-organ-prolapse.cfm

[40] Jens-Erik Walter, MD, Montreal QC et al. Transvaginal Mesh Procedures for Pelvic Organ Prolapse. Sogc Technical Update. J Obstet Gynaecol Can 2011;33(2):168-174

THE TROUBLED HISTORY OF TRANSVAGINAL POLYPROPYLENE MESH[41]

The decades of experience in treating abdominal hernias with synthetic mesh had been very eventful and a great deal had been learned. The early use of heavy meshes with small pore sizes resulted in concerning high complication rates. Reports on abdominal mesh surgery (hernias) dating back to the mid-1990s demonstrated 30-50% rates of wound complications, with reports of pain and loss of abdominal wall compliance occurring up to 50% of the time. [42]

By the late 1990s, it had become evident that the implantation of synthetic meshes was associated with an often severe foreign body reaction, resulting in acute and chronic inflammation, contraction of the mesh, infection, pain, and loss of function. Also by the late 1990s, it had been shown that there these compilations were a result of material defects, including mesh pore size and weight. Small pore size allowed bacteria safe harbor from white blood cells. Small pore size also allowed scar tissue to jump over the pore (bridging fibrosis), worsening mesh contraction and loss of body function. Prior to the year 2000, it was generally accepted that mesh pore size should be a minimum of 75 microns. By the year 2000, lightweight meshes with larger pores had replaced the older and more dangerous heavier, smaller pore meshes. By 2002 the material science world was aware that pore size would need to be, at a minimum, 1000 microns (and preferably 2000 microns) to prevent bridging fibrosis with

---

[41] See Klosterhalfen B, Junge K, Klinge W. The lightweight and large porous mesh concepts for hernia repair. Expert Rev Med Devices. 2005 Jan; 2(1):103-17; Klosterhalfen B, Junge K, Klinge W. The lightweight and large porous mesh concepts for hernia repair. Expert Rev Med Devices. 2005 Jan; 2(1):103-17; Agresta F, Baldazzi G, Ciardo et al: Lightweight partially absorbable monofilament mesh (polypropylene/poliglecaprone 25) for TAPP inguinal hernia repair. Surg Laparosc Endosc Percutan tech 2007, 17; 91- 94; Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia (1997)1:15-21; Bellon J, Honduvilla N, Jurado F et al: In vitro interaction of bacteria with polypropylene/ePTFE prostheses. Biomaterials, 2001 Jul; 22(14):2021-4; Bouikerrou M, Boulanger L, Rubod C et al: Study of the biomechanical properties of synthetic implanted in vivo. European. J. Obstet & Gynecol and Repro Bio 134: (2007)262-267; Klinge U, Klosterhalfen M, Muller A et al: Shrinking of polypropylene mesh in vivo: an experiment study in dogs, European Journal of Surgery Volume 164, Issue 12, pages 965–969, December 1998; Klinge U, Klosterhalfen B, Muller M et al: Foreign body reaction to meshes used for the repair of abdominal wall hernias. Eur J Surg. 1999 Jul; 165(7):665-73; Klinge U, Klosterhalfen B, Birkenhauer V: Impact of polymer pore size on the interface scar formation in a rat model. J. Surgical Research 103, 208-214 (2002); Klosterhalfen B, Klinge W, Schumpelick V: Functional and morphological evaluation of different polypropylene- mesh modifications for abdominal wall repair. Biomaterials. 1998 Dec; 19(24):2235-46. Krause H, Galloway S, Khoo S et al: Biocompatible properties of surgical mesh using an animal model. Aust N Z J Obstet Gynaecol. 2006 Feb; 46(1):42-5; Mamy L, Letouzey V, Lavigne J et al: Correlation between shrinkage and infection of implanted synthetic meshes using an animal model of mesh infection. Int Urogynecol J. 2011 Jan; 22(1):47-52; Garcia M, Ruiz V, Godoy A, et al: Differences in polypropylene shrinkage depending on mesh position in an experimental study. American Journal of Surgery Vol 193, Issue 4, April 2007, p538- 542; Cappelletti M, Attolini G, Cangioni G, et al. The use of mesh in abdominal wall defects. Minerva Chir. 1997 Oct; 52(10):1169-76; Klosterhalfen B, Klinge W, Hermanns B et al: Pathology of traditional surgical nets for hernia repair after long- term implantation in humans. [ABSTRACT] Chirugr 2000; 71:43-51; Seker D, Kulacoglu H. Long-term complications of mesh repairs for abdominal wall hernias. J Long Term Eff Med Implants. 2011; 21(3):205-18; Cobb W, Burns J, Peindl R et al: Textile analysis of heavy weight, mid-weight, and light weight polypropylene mesh in a porcine ventral hernia model. J Surgical Research 136, 1-7 (2006); Pandit A, Henry J. Design of surgical meshes - an engineering perspective. Technol Health Care. 2004; 12(1):51- 65; Pierce L, Grunlan M, Hou Y et al: Biomechanical properties of synthetic and biologic graft materials following long-term implantation in the rabbit abdomen and vagina. Am J Obstet Gynecol. 2009 May; 200(5):549.e1-8; Costello C, Bachman M, Grand, S, et al. Characterization of heavyweight and lightweight polypropylene prosthetic mesh explants from a single patient. Surg Innov. 2007Sep; 14(3):168-76.

[42] O'Dwyer PJ, Kingsnorth AN, Molloy RG, et al. Randomized clinical trial assessing impact of a lightweight or heavy- weight mesh on chronic pain after inguinal hernia repair. Br J Surg 2005;92:166–170.Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591. Klosterhalfen, B, Klinge, U. Schumpelick, V. Functional and morphological evaluation of different polypropylene –mesh modifications for abdominal wall repair. Biomaterials 19.1998. 2235-46

resultant contraction and loss of function.[43] Although meshes became lighter and more porous, complications associated with the severe foreign body reactions persisted. The material science literature and the medical device industry became aware that surgical meshes were still too heavy, were still shrinking as much as 85%, and were not providing the necessary compliance (stretch). Between 2006 and 2008, the biomaterial science world learned that the majority of commercialized meshes lost the pores, once implanted. Once placed under load, the meshes would deform and pores would disappear. Since 2007, it has been understood that mesh needed an "effective porosity" of greater than 1000 microns (1000 microns under load after implantation).[44] Patients continued to suffer from the resultant acute and chronic inflammation (described by material scientists as a chronic wound behavior), mesh contraction, pain, and loss of function. Change was needed. Unfortunately, by this time, synthetic mesh was being marketed for vaginal surgery, the treatment of pelvic organ prolapse, where the consequences of the material defects would be much graver.

If the synthetic meshes used for abdominal hernias were to be used in vaginal surgery, not only would it be necessary to use a light weight mesh with sufficient effective pore size that could maintain a minimum of 15-30 % stretch, but it would be necessary to demonstrate that the benefits outweighed the risks. Any device company considering the marketing of synthetic mesh for transvaginal pelvic organ prolapse surgery would need to demonstrate both that it provided a benefit over the proven native tissue surgeries and that the known complications of synthetic mesh, including complications that had been well established in the abdominal hernia literature (severe acute inflammation, chronic inflammation, contraction, infection, loss of function, and pain), did not have an adverse impact on bowel, bladder, or coital (intercourse) function.

Evidence of safety and efficacy could only come from extensive testing and clinical trials. The types of testing and clinical trials to be performed both prior to marketing and following the initial marketing of a medical device are governed by both federal laws (FDA) and corporate guidelines. The FDA provides a set of laws and guidance documents that establish the minimum pre-market and post-market safety and efficacy testing that must be performed and reviewed to its satisfaction. Any company failing to demonstrate safety and efficacy in accordance with the FDA rules and regulations cannot legally market its medical device in the United States. Other nations have similar rules and regulations (ISO). Failure to provide post-market evidence of safety and efficacy data required by the FDA leads to the loss of the right to legally market a device in the United States. Beyond the minimum federal requirements, manufacturers of medical devices establish their own set of guidelines and minimum requirements that must be adhered to prior to and following the initial marketing of their medical devices. Such manufacturer's guidelines and requirements

---

[43] Klinge, U., B. Klosterhalfen, V. Birkenhauer, K. Junge, J. Conze, and V. Schumpelick. "Impact of Polymer Pore Size on the Interface Scar Formation in a Rat Model." Journal of Surgical Research 103.2 (2002): 208-14.

[44] Mühl, Thomas, Marcel Binnebösel, Uwe Klinge, and Thomas Goedderz. "New Objective Measurement to Characterize the Porosity of Textile Implants." Journal of Biomedical Materials Research Part B: Applied Biomaterials J. Biomed. Mater. Res. 84B.1 (2007): 176-83.

typically provide for important safety and efficacy testing, often beyond that required by Federal rules and regulations. This often includes testing and clinical trials ordinarily required by Federal Rules and regulations that can be circumvented by crafty manufacturers in their rapid commercialization of a device. One should be aware that medical device safety and efficacy is provided by way of both federal rules and regulations and medical device industry standards.

INTELLECTUAL PROPERTY

The Invention of PROLIFT:

On **March 1st of 2002**, French surgeon, Dr. Bernard Jacquetin, filed a U.S. provisional patent application (and PCT application) for his novel method and apparatus for treating pelvic organ prolapse. Dr. Jacquetin's non-provisional USPTO utility application, METHOD AND APPARATUS FOR TREATING PELVIC ORGAN PROLAPSES IN FEMALE PATIENTS, was filed on **February 28th, 2003**.[45] This application disclosed a four armed anterior implant, a two armed posterior implant, and a single implant represented by a combination of the anterior and posterior implant (The preferred material proposed by Jacquetin was a single sheet to mesh. He gives the example of soft PROLENE of Ethicon). Dr. Jacquetin not only disclosed the multi-armed mesh shapes later marketed by Ethicon as PROLIFT, but also disclosed the method of using trocars to pull the mesh arms through the obturator foramen, as well as through the buttocks. On **November 6th of 2006** the USPTO granted patent number US 7,131,944 B2.[46] This patent granted 29 claims. These claims included implants with either two or four arms for treating a cystocele, an implant with two arms treating a rectocele, and a single implant that combined the former two. This patent also granted claims for methods of implanting these novel armed devices that included pulling arms through the obturator foramen and attaching arms to the sacrospinous ligaments. In addition to these granted claims, the published patent included important teachings by the inventor, Dr. Jacquetin.

- **"**When the endopelvic fascia is strong, the straps can be severed from the anterior implant, thereby avoiding the trans-obturator passage. In such a situation, the anterior implant would be fixed laterally by two stitches on each of its sides." Dr. Jacquetin herein discourages the use of arms based on intra-operative findings.
- "Since a complete dissection of the arcus tendinosus fascia pelvis is unnecessary, the finger feels the obturator foramen through the muscular pelvic side wall". Dr. Jacquetin herein discourages disruption of the level 2 vaginal support (discourages the creation of a paravaginal fascial defect).

[45] US 60/361,503

[46] US 7,131,944 B2

- "Plication of the Pre-Vesical Fascia. This procedure is typically performed using a continuous suture of 2/0 absorbable mono filament suture. Plication of the Pre-Rectal Fascia. This procedure is typically performed using a continuous suture of 2/0 absorbable monofilament suture." Dr. Jacquetin herein teaches that native tissue repair should be performed concurrently with mesh implantation.
- "The braided sutures are then used to attach their associated straps (arms) to the sacrospinous ligament." Although Dr. Jacquetin also discloses a passage through the buttock and sacrospinous ligament, such disclosure is neither enabling, nor claimed.
- "The angle is spherically selected so as to reduce the amount of rectal constriction in the event that the posterior implant shrinks when implanted in a patient's body." Dr. Jacquetin herein warns of constriction of the mesh arms around the rectum.
- "A vaginal vault suspension can be performed using the anterior implant 10 and/or the posterior implant." Dr. Jacquetin herein teaches three methods of apical suspension:
    1. "[A]ttaching the vaginal wall to the anterior implant and or posterior implant."
    2. "[A]ttachment between the uterosacral ligaments and the anterior implant and or the posterior implant."
    3. "[T]he vaginal vault is fixed independently of either of the implants 10, 50 by a standard bilateral sacrospinous fixation."
- "The anterior implant and the posterior implant may be provided in a variety of standard shapes and sizes (e.g., small, medium, and large). After comparing these standard implants to the pelvic anatomy of a particular patient, the surgeon would select the one which best meets the patient's needs. If any modifications to the size and/or shape of the selected implant are required, they can be effected by the surgeon in the surgical arena." Dr. Jacquetin herein teaches that a one-size implant will not fit all patients and, even after picking the size best suited for the patient's anatomy, further modification may be needed to custom fit the implant to the patient's anatomy.

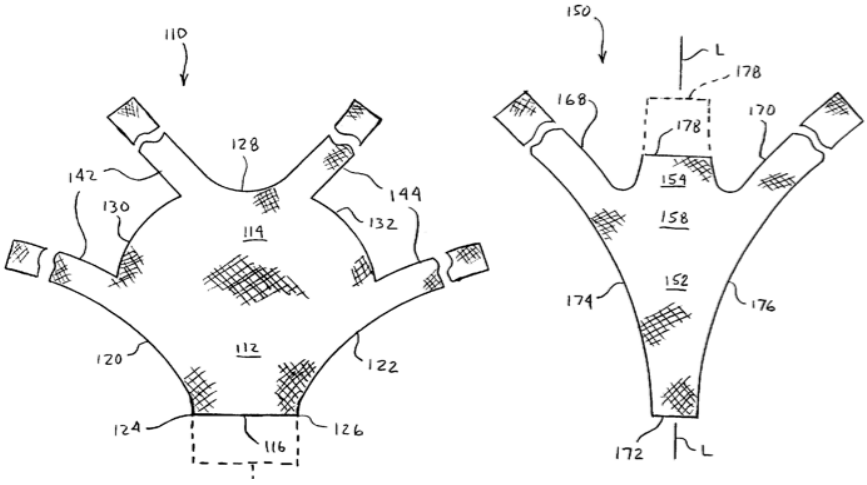


FIGURE 1
TWO EMBODIMENTS OF SHOWN BY INVENTOR[47]

Assignment of Intellectual Property:

On **February 13th of 2003**, Dr. Bernard Jacquetin signed a consulting agreement with Ethicon.[48] In this agreement, Dr. Jacquetin agreed to assign to Ethicon the rights associated with patent application METHOD AND APPARATUS FOR TREATING PELVIC ORGAN PROLAPSES IN FEMALE PATIENTS, all existing and subsequent improvements, and all clinical data relating thereto. In addition, he agreed to provide consulting services. In consideration for such, Ethicon agreed to pay Dr. Jacquetin "3% of the "net sales" of any device covered in whole or in part by at least one bona fide, valid claim of an unexpired patent resulting from the patent applications or any foreign counterpart thereto." Dr. Jacquetin would also receive one thousand USD per day and ten thousand USD upon the effective date of the agreement. On **October 29th of 2004**, Dr. Jacquetin assigned his U.S. patent application to Ethicon.

Other Invention:

On **September 15th of 2004**, Ethicon filed a patent application with the USPTO for a device and method for implanting armed mesh.[49] On May 5th of 2009, the USPTO granted patent US 7,527,588 B2, SYSTEM AND METHOD FOR SURGICAL IMPLANT PLACEMENT. In this patent disclosure, Ethicon taught a device and method for using such device, as well as a method for using the device in association with the procedure taught by Dr. Jacquetin in his patent US 7,131,944 B2. The subject device of this patent is used for the implantation of PROLIFT. In its patent disclosure, Ethicon teaches the PROLIFT guide (trocar), cannula (sheath over trocar), and retrieval element and is

[47] US 7,131,944 B2
[48] ETH-10964
[49] 10/941,241

granted claims for the described three-part device, the method of its use, and its use for the anterior PROLIFT procedure. In addition to the claims describing the device and its method of use, Ethicon provided other important teachings:

- Ethicon references Dr. Jacquetin's patented method and offers its novel device as a solution to a problem. "Difficulties have been encountered, however, in pulling the strap-like mesh extensions through the pelvic cavity. In particular, the mesh extensions (arms) can cause tearing of tissue as they are pulled through, which can cause additional pain, bleeding, and/or nerve damage, but can also lead to improper positioning of the implant." Ethicon herein teaches that the mesh arms are in proximity to nerves and blood vessels and placement may result in pain, bleeding, and/or nerve damage.
- "Other features that may be added include one or more radio opaque markings to enable visualization after placement using fluoroscopy or x-ray, or the addition of regularly spaced markings along the length of the cannula to allow the user to determine how far the cannula has been inserted into the patient's body, and also to determine whether the cannula position has changed following its initial placement." Ethicon herein teaches device features that may increase surgical success and decrease complications.
- "In an alternative embodiment, the cannula could be a dual channel cannula having a cross-section such as that shown in FIG. 6b. The first channel would be dimensioned to receive the guide needle as described above, and the second channel dimensioned to receive the retrieval line." Herein Ethicon taught a device feature that would maintain the integrity of the cannula shape and patency during mesh arm retrieval and hence discourage deformation (e.g. curling or roping) of the mesh arms.

THE PROLIFT PATH TO MARKET

In its commercialization of the PROLIFT device, Ethicon contended with both internal (corporate) and external (U.S. and International) standards and policies.

Quality Systems:

There are several reasons medical device manufacturers create policies and procedures to maintain safety and quality. The first is most obvious, to protect the consumer. The second is also obvious, to protect the company. In the United States, there is a third reason, the 1997 addition to the FDA's CGMP of "Quality System (QS) Regulation/Medical Device Good Manufacturing Practices" (21 CFR Part 820). These guidelines provide the minimum requirements a device manufacturer must meet to assure quality and safety to the end user. Although the FDA quality system (QS) sets mandatory guidelines, it does state:

> *"Manufacturers should use good judgment when developing their quality system and apply those sections of the QS regulation that are applicable to their specific products and operations, 21 CFR 820.5 of the QS regulation. Operating within this flexibility, it is the responsibility of each manufacturer to establish requirements for each type or family of devices that will result in devices that are safe and effective, and to establish methods and procedures to design, produce, distribute, etc. devices that meet the quality system requirements".*[50]

The FDA built its guidelines to be consistent with a voluntary set of international quality systems guidelines set by the International Organization for Standards (ISO). While compliance with ISO 13485 and 14971 and ISO certification is voluntary, the overwhelming majority of device manufacturers achieve compliance and certification (as most international customers demand such).[51]

One component of a QS system is the Device Design Safety Assessment (DDSA). As part of the DDSA, a company that endeavors to protect the consumer, protect itself, be in compliance with CGMP, and achieve ISO certification, establishes a Device Failures Modes and Effects Analysis policy (dFMEA) and an Application Failure Modes and Effects (aFMEA) Policy. It is important to note that, as the FDA QS was based on the ISO, the concepts contained in the FMEAs typically satisfy both the FDA QS mandate and the voluntary international guidelines expected by device customers. Ethicon indeed had in place such policies. Ethicon created a Company Procedure for Medical Device Risk Management which was eventually re-written to "better align to ISO 14971".[52] Ethicon's mandate with regard to its DDSA and FMEA procedure stated "the requirements defined by this procedure must be completed prior to first human use." The DDSA serves as the foundation for assessment of device design risk. Risk Management culminates in a demonstration of safe and effective device use through the design validation process (Ethicon DDSA and FEMA).[53]

The PROLIFT Application Failure Modes and Effects Analysis:

A typical method employed is the calculation of a Risk Priority Number (RPN). This is the method used by Ethicon in assessing the risks associated with the application of its PROLIFT device. The International Organization for Standards, (ISO) 14971, describes nearly identical methodology.[54]

The PROLIFT RPN for each potential failure (complication) was calculated, as is customary, by multiplying the severity of the complication (S) by the estimated occurrence rate (O) by the detection rate (D). All scales were 1-10 (FIGURE X, FIGURE Z). Risk Priority Numbers that resulted in two high risk categories, ALARP (as low as

---

[50] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/

[51] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/

[52] ETH.00337441

[53] ETH.MESH.03742546-47

[54] ISO 14971:2007(E)

reasonably practicable) and RBA (Risk Benefit Analysis Required) were to trigger additional actions:

> "If the item is in the ALARP or RBA category, consider ways to modify the design to either:
>
> - Eliminate the possibility of the cause occurring
> - Perform testing/analysis that will reduce the detection rating
> - Reduce the occurrence rate"[55]

Application FMEA Detection Rating Table

This table defines descriptions/ probabilities to a Rating #. Use this table to estimate how often the user will be aware that the failure mode occurred and take appropriate, reasonable action (not heroic) to prevent patient harm from occurring.

Rating #	Description	Probability of Detecting and being able to take appropriate action Note 1
1	Very Frequent	>99%
2	Very Frequent	>98%
3	Frequent	>95%
4	Frequent	>90%
5	With Moderate Frequency	>80%
6	With Moderate Frequency	>60%
7	With Low Frequency	>40%
8	With Low Frequency	>20%
9	In Frequent	>10%
10	No chance	<10%

Note 1 Actions considered should be within the confines of the existing procedure. An example would be that in most instances the need to convert an minimally invasive procedure to an open procedure is "heroic" action. Consideration should be given to the additional risks to the patient caused by the need to take these actions and may include the addition of line items.

Application FMEA Occurrence Rating Table

This table defines descriptions/ probabilities to a Rating #. Use this table to estimate how often the potential cause will occur. In the case of two or more things happening together to cause the failure mode, estimate the occurrence rate of the two or more things happening at the same time.

QUALITATIVE APPROACH *LIKELIHOOD OF HAPPENING*	RANKING	QUANTITATIVE APPROACH *Based on field performance data of similar medical device(s) under similar conditions*
Remote: Situation unlikely	1 Note 2	< 1 in 1 000 000
Low: Situation rare	2 Note 2	< 1 in 100 000
Situation relatively few	3 Note 2	< 1 in 40 000
Moderate:	4	<1 in 1 000
Situation occasionally occurs	5	<1 in 400
	6	<1 in 100
High:	7	<1 in 40
Situation repeatedly occurs	8	<1 in 20
Extreme:	9	<1 in 10
Almost inevitable	10	>1 in 10

FIGURE X[56]

[55] ETH.MESH.03742883

[56] ETH.07249

FMEA SEVERITY RANKING SCALE

NOTE: (F) denotes functional impact (A) denotes appearance impact

RANKING	DEGREE OF IMPACT
1	Improbable/Minor: Not perceptible or noticeable. (F) The consequences will not have any perceptible impact on the performance of the medical device. (A) The user will not notice the consequence.
2-3	Insignificant/Low, Negligible, Nuisance, Noticeable (F) Nuisance but likely negligible. (A) The user will probably notice only a minor negative impact on the medical device.
4-5	Moderately Significant/Dissatisfaction (A&F) The user will notice a negative impact as failure occurs, such as difficult to apply, difficult to use, discomfort, etc. (F) Partial loss of medical device operation or performs at a reduced level; possible gradual performance degradation.
6-7	Significant/High Annoyance (A&F) The failure causes greater annoyance to the user, such as creates pain. (F) Partial system function is lost, but the medical device can still be used without any safety concern.
8	Extreme/Very High: System function is lost (F) The medical device cannot be used, but failure does not create a safety, non-compliance or regulatory issue.
9	Almost catastrophic: Hazardous with warning (F) Medical device failure involves safety, non-compliance and/or regulatory issue. The user is forewarned that medical device failure is occurring.
10	Catastrophic: Hazardous without warning (F) Medical device failure involves safety, non-compliance and/or regulatory issue. The user is NOT forewarned that medical device failure is occurring.

Risk Categorization Table

SEVERITY				
	9 - 10	As Low As Reasonably Practicable	RBA Required	RBA Required
	7 - 8	As Low As Reasonably Practicable	As Low As Reasonably Practicable	RBA Required
	1 – 6	Broadly Acceptable	Broadly Acceptable	
		1 –269	270 – 600	601+
		RPN		

RBA = Risk Benefit Analysis per instructions in PR602-003

FIGURE Z[57]

Potential Failure Modes, Potential Hazards, Harm, Potential Cause, and Control Method:[58]

The following is a brief overview of the PROLIFT aFMEA table focusing on points of concern:

Potential Failure Mode: **Cannula damaged during loading.** Ethicon listed

[57] ETH.07250

[58] ETH.07291-07295

"increased resistance to strap" (mesh arm) and "increased resistance to placement in patient" as the hazards. Ethicon stated that the potential harm was bleeding and a prolonged procedure. Ethicon offered as a control method "IFU." Yet, neither the IFU published following the aFMEA, nor subsequent revisions provided any teaching to decrease the occurrence of this failure or increase the identification of such. Furthermore, the associated hazards of increased tissue resistance (with damage to patient tissue) and increased strap resistance (with strap damage and risk of device failure) were not disclosed in the IFUs. Finally, Ethicon did not offer the simple and free corrective action, "if damage occurs to a cannula, discard the cannula and use one of the extra cannulas".

Realized results of this uncontrolled failure (complication) include rolling or other deformity of the strap (mesh arm) with acute and chronic pelvic pain, dyspareunia and pain with ambulation; trauma to the muscles and nerves of the pelvis with acute and chronic pelvic, groin, and leg pain syndromes, and tearing or avulsion of the mesh strap (recognized and unrecognized) with resultant persistent or recurrent pelvic organ prolapse.

Potential Failure Mode: **Incorrect passage of proximal Anterior Cannula** with effects, hazards, and harms described as injury to vital organs, including bleeding, partial paralysis, infection and recurrence. Ethicon listed as the root cause "lack of training or skill." Ethicon rated the severity of this failure to be an 8-9 (extreme-almost catastrophic). Yet, its recommended control method for this extreme -almost catastrophic- failure was to have the IFU recommend additional training. Ethicon neither stipulated that that training be required to decrease the risk of catastrophic failure, nor limited marketing to highly skilled users. Of additional note, the RBN score for many of the harms created by this failure was in the "ALARP" category that should have triggered a risk benefit analysis.[59] However, the FMEA table shows that no further action was taken. Furthermore, ISO points out that a numeric calculation (e.g. RPN) must be looked at both objectively and subjectively as a failure resulting in severe harm with a low occurrence, which may result in an unacceptable risk benefit analysis (even though its risk score may not be high).[60]

Realized results of this uncontrolled failure (complication) include bowel perforation and possible death; bladder perforation (recognized and unrecognized) with acute and chronic bladder pain, urinary tract infections, vesicovaginal fistula formation (a tunnel between bladder and vagina that causes leakage of urine into vagina), overactive bladder, and urgency incontinence of urine; injury to the obturator nerve with acute or chronic pelvic pain, pain with ambulation and or difficulty with ambulation; injury to the obturator blood vessels with hemorrhage and blood transfusion with

[59] ETH.07292

[60] ISO 14971:2007(E) 23-59

possible death, and dyspareunia.[61]

Potential Failure Mode: **Incorrect passage of distal Anterior Cannula** with effects, hazards, and harms described as injury to vital organs, including bleeding, partial paralysis, infection and recurrence. Ethicon's findings and omissions herein are identical to those cited for passage of the proximal anterior cannula (previously discussed). However, realized results of this uncontrolled hazard (complication) include, in addition to those cited for the proximal anterior cannula, injury to the urethra, erosion of mesh into the urethra, placement of mesh into the urethra, urethral obstruction, and urethrovaginal fistula.

Potential Failure Mode: **Incorrect passage of Posterior Cannula** with effects, hazards and harms described as injury to vital organs, including bleeding, partial paralysis, infection and recurrence. Ethicon's findings and omissions herein are identical to those cited for passage of the Anterior Cannula (previously discussed).

Realized results of this uncontrolled failure (complication) include bowel perforation and possible death; rectal perforation (recognized and unrecognized) with acute and chronic rectal pain, chronic constipation, rectovaginal fistula formation (a tunnel between rectum and vagina that causes leakage of stool into vagina), fecal incontinence; injury to the pudendal nerve with acute or chronic pelvic pain, pain with ambulation and or difficulty with ambulation; injury to the pudendal blood vessels with hemorrhage and blood transfusion with possible death, and dyspareunia.

Potential Failure Mode: **Removal or displacement of cannula** with effects, hazards, and harm of procedural delay, "additional tissue trauma," and bleeding. Ethicon offered a control method of "IFU." Yet, neither the IFU published following the completion of the FMEA, nor subsequent IFUs provided any teaching to decrease the occurrence of this hazard or teaching of how to handle this complication when it occurs.

Realized results of this uncontrolled failure (complication) include all those described for incorrect placement of cannula. In the event of a partially displaced cannula, the natural tendency of the surgeon is to try to push the cannula back in. As there is no longer an obturator (a rigid guide), the blunt tipped cannula cannot be effectively and predictably guided through the pelvis. This results in blunt trauma to the muscles, nerves, and blood vessels of the pelvis as well as inaccurate passage of the cannula.

Potential Failure Mode: Removal of too much mesh material, no

[61] Realized results represent complications that have occurred and have either been documented in the FDA MAUDE database, reported in the medical literature, or complications I have evaluated and often treated in my pelvic medicine center. Many of these realized results represent failure related harm that was not evaluated by Ethicon in its FEMA.

adjustment to mesh material (when one is required), or insufficient adjustment of mesh material (when one is required) with effects, hazards, and harm of bunching of mesh, erosion, and recurrence of prolapse. Ethicon rated the severity of this failure to be an 8 (extreme/very high). Yet, its recommended control method for this extreme failure was to have the IFU recommend additional training. Ethicon neither stipulated that that training be required to decrease the risk of extreme failure, nor limited marketing to highly skilled users. Ethicon provided no teaching in its IFU with regard to removal or adjustment of the mesh material. The IFU, however, referred to an additional label not included with the PROLIFT device, the Surgical Technique document. The Surgical Technique provided only that the implant should be "tension free" and "If required, small reductions in the dimensions of the Total Implant to ensure proper fit should be performed."[62] This teaching, not included with the IFU, is ambiguous and in no way mitigates or controls this identified extreme failure. Of additional note, the RBN for many of the harms created by this failure was in the "ALARP" category that should have triggered a risk benefit analysis.[63] However, the FMEA table shows that no further action was taken. Furthermore, ISO points out that a numeric calculation (e.g. RPN) must be looked at both objectively and subjectively as a failure resulting in severe harm with a low occurrence that may result in an unacceptable risk benefit analysis (even though its risk score may not be high).[64]

Realized results of this uncontrolled failure (complication) include mesh exposures (also known as extrusions), multiple mesh exposures, patient and partner pain with intercourse (dyspareunia), inability to have intercourse (often chronic), acute and chronic vaginal bleeding and discharge, and device failure with persistent or recurrent pelvic organ prolapse.

Potential Failure Mode: Implant installed incorrectly (recognized and unrecognized) with effects, hazards, and harm listed as only delay in surgery, repeat surgery, and recurrence of prolapse. Ethicon rated the severity of this failure (when unrecognized) to be an eight (having an "extreme/very high impact") and calculated the RPN to be in the ALARP range.[65] There is no evidence that the required risk-benefit analysis occurred. Although Ethicon indicated that the IFU would be used to control for this extreme failure, neither the original IFU, nor subsequent updates provide significant teaching of an appropriately installed implant (e.g. photographs of correctly and incorrectly installed implants).

Realized results of this uncontrolled failure (complication) include vaginal mesh exposure with resultant acute and chronic pain, bleeding, discharge, and

---

[62] ETH-07252, ETH-07282

[63] ETH.07294

[64] ISO 14971:2007(E) 23-59

[65] ETH.07294

dyspareunia, erosion of mesh into bowel and bladder with resultant fistula formation, urinary incontinence, fecal incontinence, constipation, vaginal shortening and deformity with resultant chronic dyspareunia or apareunia (pain with intercourse or inability to have intercourse), and surgical failure with recurrent or persistent pelvic organ prolapse.

Potential Failure Mode: implant placed with too much tension or insufficient tension with effects, hazards, and harm listed only as tissue erosion and recurrence. Ethicon identified the cause as lack of surgeon training or skill and offers as a method of controlling for this failure "IFU (recommends professional education training)." Ethicon once again failed to recognize substantial, and in this case perhaps catastrophic, consequences of a failure mode. Tension results in acute and chronic pelvic pain, acute and chronic pain with intercourse, acute and chronic urinary retention, acute and chronic rectal pain and constipation, and acute and chronic pain with ambulation. These harms were extensively realized in the field. As noted elsewhere herein, an IFU that recommends training in no way communicates the consequences of not receiving such training, nor mandates such training. As discussed elsewhere in this monograph, neither the "professional training," nor other labels offered a validated and reproducible method for intraoperative tension assessment.

There is a clear trend of within the FEMA for Ethicon to understate the effects and harms associated with potential failures, not offer effective controls, and not offer evidence of a meaningful risk benefit analysis for failures with high RBN scores. Perhaps even more concerning is that the most common failure control method, "IFU", was never utilized to control these failures. The addition of spare cannulas, IFU updates with descriptions and photos of failures (with instructions for managing failures), and a restriction of marketing to "skilled" surgeons are examples of simple, cost-effective failure controls that were not implemented. In addition, very harmful failures, such as contraction of the mesh and untreated compartment failure, are failure modes that were known to those skilled in the art, but not explored in the FEMA (contraction occurs in all cases of PROLIFT implantation and untreated compartment failure may occur in up to 40% of cases[66]). Contraction is an insidious process with catastrophic consequences. An email to PROLIFT project manager and FEMA team member, Scott Ciarrocca, dated November of 2003, reflects an ignored request to add contraction to the DDSA.[67] The FEMA protocol mandates a risk-benefit analysis for such failure modes. No such analysis was performed.

Piet Hinoul, M.D., Ph.D., Ethicon's Vice President of Medical Affairs and former Director of Medical Affairs-Worldwide, testified with regard to Ethicon's DDSA and

---

[66] Milani AL, Withagen MIJ, Vierhout ME. Outcomes and predictors of failure of trocar-guided vaginal mesh surgery for pelvic organ prolapse. Am J Obstet Gynecol 2012;206:440.e1-8.

[67] See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey, Exhibit 621

FEMA policies.[68] Dr. Hinoul testified that his comments with regard to the DDSA applied to the FEMA.[69]

> *"Q Are you aware of when that is utilized in terms of prelaunch or after the product is launched?*
>
> *A Well, this is probably the design safety -- there is a system where we try to capture all the possible things that can go wrong and capture them and how we're going to mitigate those risks. That is probably part of that.*
>
> *Q And that is prelaunch, before the product is put on the market; correct?*
>
> *A Yes, while it's being designed and then before it goes to the market, yes.*
>
> *Q And the purpose of the DDSA (and FEMA) from the perspective of medical affairs is to capture all the things that can go wrong, as you just stated?*
>
> *A Yes.*
>
> *Q And then to attempt to mitigate each of those potential adverse events before the product goes on the market so that people won't be harmed; correct?*
>
> *A Right. Or limit it or how you can assure that if that -- how you can try to mitigate that complication. It doesn't mean that you can completely rule it out.*
>
> *Q The methods to mitigate a complication primarily are to either warn or instruct so that people will either be aware of it and avoid it --*
>
> *A Uh-huh.*
>
> *Q -- or to change the design so that the adverse event won't occur; correct?*
>
> *A Right. Those possibilities, yes.*
>
> *Q And if an adverse event cannot be mitigated either through warnings and instructions or through design change, then what does Ethicon medical affairs recommend be done with that product?*
>
> *A Then the role of medical affairs is to assess how high the likelihood of that occurring would be. And as I – you know, so it's a weighing of the risks at that point."*[70]

Dr. Hinoul, testifying as Ethicon's World Wide Director of Medical Affairs, makes it

---

[68] See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey

[69] See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey. Pg. 421

[70] See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey. Pg. 365-367

clear that Ethicon's purpose for the DDSA (FEMA) is to identify "all the things that can go wrong" with PROLIFT and mitigate those risks prior to the marketing of PROLIFT. He also makes it clear that such mitigation should have taken place either through labeling or device modification. Dr. Hinoul also indicates that he is aware of the Ethicon DDSA (FEMA) policy that stipulates that his division, Medical Affairs, must weigh the risks of complications that cannot be effectively mitigated against potential benefits. Yet, as noted previously, there is no evidence such risk/benefit analysis took place within the FEMA process. When asked if there was an objective means by which Medical Affairs decided if a risk outweighed a potential benefit, Dr. Hinoul stated, "It is why -- that's why it is medical affairs -- that's why medical affairs give the input, because it is going to be based on clinical experience and it's going to be based on how we feel -- it may be a serious adverse event as we capture it, but what are the clinical implications in the long run and what are the chances of those serious long-term implications happening as opposed to just a complication being noted."[71] Dr. Hinoul also agreed that an exclusion from the DDSA of an "adverse event serious complication" that was known by medical affairs, would flaw the DDSA.[72] Ethicon was well aware of the serious and common complication of mesh contraction and knowingly opted not to include such in its FEMA process.[73] Dr. Hinoul further stated, "So I'm testifying for medical affairs and medical affairs indeed has always been aware of a risk of contraction."[74] Additional testimony from Dr. Hinoul makes this deliberate omission of the contraction problem even more concerning:

> *"Q Okay. You knew that significant retraction could occur?*
>
> *A Right.*
>
> *Q Okay. And you knew that a significant retraction could lead to pain for the patient; correct?*
>
> *A Yes.*
>
> *Q You knew it could lead to recurrence; correct?*
>
> *A Yes.*
>
> *Q You knew it could lead to erosion; correct?*
>
> *A Yes.*
>
> *Q You knew it could lead to dyspareunia; correct?*

---

[71] See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey. Pg. 368

[72] See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey. Pg. 376

[73] See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey, Pgs 364-365 and Exhibit 621

[74] See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey. Pg. 379

A Yes."[75]

Asked if he felt that the omission of contraction from the DDSA represented a flaw in the DDSA, Dr. Hinoul stated "So it would be – we would have, according to – following this email, it would be appropriate to follow up on retraction (contraction)".[76]

Scott Ciarocca, Ethicon's director of R&D and the FEMA project leader, confirmed that medical affairs was responsible for creating the list of failures (hazard to be evaluated) and that medical affairs chose those hazards, in its opinion, it deemed appropriate.

"Q. Who determined what hazards to list?

A. That would have been primarily a function of medical affairs.

Q. You would want to make sure that the hazards listed would encompass each of the foreseeable hazards with use of the product so you could make sure that you assess each of the hazards. Correct?

A. It would list what in medical affairs' opinion is an appropriate list of hazards as it relates to many things. [77]

Q. For the DDSA to be used to its fullest intended extent, each of the known hazards for the product need to be assessed as part of the DDSA. Correct?

A. Yes."[78]

Ethicon's QS, DDSA with FEMA procedures, followed a flowchart.[79] One of the earliest nodes (steps) is that of "Identify Hazards." After identifying the hazards of the device and application, the risks of each hazard must be estimated. Those risks rated as IV or V are subject to the FEMA procedure. As stated by the PROLIFT FEMA project leader and Director of R&D, the identification of risks was performed by Medical Affairs. Although Ethicon's Director of Medical Affairs testified that one of the functions of Medical Affairs (in the DDSA and FEMA procedure) "is to capture all the things that can go wrong," including multiple severe and critical failures and hazards (IV and V) related to the polypropylene mesh and well known to be associated with the material, including small pore size, loss of pore size (effective pore size), degradation, contraction (retraction), and loss of elasticity, were not captured by Medical Affairs. The flowchart requires all level IV and V risks to undergo a Risk Benefit Analysis. Risk Benefit Analysis was to be performed and recorded (DHF) under the supervision of

---

75 See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey. Pg. 382-383

76 See deposition of Piet Hinoul, M.D. Ph.D, April 2012. Superior Court of New Jersey. Pg. 383

77 48 Scott Ciarocca dep., 339:6-24

78 Scott Ciarocca dep., 342:16-343:3

79 ETH.MESH.03742551

the Medical Director.[80] If the overall risk was unacceptable, the risk assessment was to end and a re-design was required. As the above-known noted material defects of the GYNEMESH PS polypropylene mesh were not included by Medical Affairs in the DDSA and FEMA, there was no associated risk-benefit analysis. Additionally, as noted above, the ALARP categorization of the RPN associated with failures of cannula passage, guide removal, mesh adjustment, and tensioning all required risk- benefit analysis. However, I can find no evidence of such. Only after completion of the FEMA and acceptable Risk Benefit analyses does the flowchart provide that the team may "Go on to evaluating the overall risk. The team assessing the design risk must conclude the assessment with a decision whether or not the reviewed device risk is acceptable for its intended use."[81] Each team member must sign the DDSA approval page and the Medical Director or delegate must approve the final version. "The DDSA must be approved prior to Design Transfer or first human use."

Expert Opinion on Path to Market:

Ethicon created a QS (quality system), including a DDSA and FEMA procedure, that was designed to align with the voluntary international standards (ISO) and the U.S. guidelines, 21 CFR Part 820. Ethicon deviated from its own mandatory DDSA and FEMA procedures by failing to include known failures (hazards or complications) in its DDSA, by failing to document the required risk-benefit analyses of such known failures/hazards, by failing to document the required risk-benefit analyses of failures/hazards with high risk scores (RPN), and by not implementing controls for the identified failures/hazards. It was only by deviating from and violating the rules of its own QS system that Ethicon was able to use the experimental PROLIFT in humans.

COMPLIANCE AND NONCOMPLIANCE WITH MEDICAL, INDUSTRY, AND REGULATORY STANDARDS

The Medical Device Amendments of 1976 set the regulatory rules by which the FDA still governs. These amendments divided devices into either Pre-Amendment or Post-Amendment devices. Those that were on the market prior to the amendment, Pre-Amendment devices, were grandfathered and did not need to undergo the new Pre-Market review process. Post-Amendment devices would have to undergo a Pre-Market Approval (PMA) process.[82] The PMA "is the most stringent type of device marketing application required by FDA." The PMA application has a Non-clinical Laboratory Studies' Section and a Clinical Investigations' Section. The Non-clinical laboratory studies' section "includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests. Non-clinical studies for safety evaluation must be conducted in compliance with

[80] Eth.Mesh.00337457

[81] ETH.MESH.03742560

[82] Alex Gomelsky and Roger R. Dmochowski. Biocompatibility Assessment of Synthetic Sling Materials for Female Stress Urinary Incontinence. JUrol. Vol. 178, 1171-1181, October 2007

21CFR Part 58 (Good Laboratory Practice for Nonclinical Laboratory Studies)." The Clinical investigations section "includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations."[83] The pathway to PMA is lengthy and costly. Device companies often spend millions of dollars and several years prior to completing the PMA process.

The bad news for patients and the good news for device companies is that the Medical Device Amendments of 1976 allow Medical Devices, such a slings, to bypass the PMA process by successfully completing something known as the 510K or Pre-Market Notification process. A 510K approval is obtained from the FDA when a device company demonstrates that their device is substantially equivalent to any device already being legally marketed. Such a device is called the "Predicate Device." This Predicate Device may be any one of the thousands of Pre-Amendment devices (that never underwent the scrutiny of a PMA), a Post-Amendment device that obtained a PMA, or a Post-Amendment device that never obtained a PMA but is already legally marketed. A legally marketed Post-Amendment device that never obtained a PMA is any device that was able to show substantial equivalence to another device that is being legally marketed.[84] In summary, a device can be marketed by a device company, if that company can show that its device is substantially equivalent to a device that was found to be substantially equivalent, and so on, to a device that was found to be substantially equivalent to a Pre-Amendment device that never underwent the scrutiny required under the PMA process. Of course, a device company can also opt not to claim its new device as substantially equivalent to an un-scrutinized predicate and voluntarily submit its device to the required Non-clinical Laboratory Studies and Clinical Investigations required to achieve a PMA, or alternatively, perform such studies voluntarily in parallel to the 510(k) process.

Ethicon chose not to subject its new product to the rigorous scrutiny required for FDA Pre-Market Approval (PMA). Of even greater concern, Ethicon chose to circumvent the 510 (k) FDA pre-market clearance process. Through its curious internal rational for bypassing both of these regulator pathways, Ethicon was able to avoid extensive animal and human trials, avoid the testing required in the demonstration of substantial equivalence, and proceed rapidly to market without FDA clearance.

---

83 "U.S. Food and Drug Administration." Premarket Approval (PMA). N.p., n.d. Web. 11 Nov. 2015. http://www.fda.gov/Medicaldevices/Deviceregulationandguidance/Howtomarketyourdevice/Premarketsubmissions/Premarketapprovalpma/Default.Htm

84 "Overview of Medical Devices and Their Regulatory Pathways." Overview of Medical Devices and Their Regulatory Pathways. N.p., n.d. Web. 11 Nov. 2015. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm203018.htm, "U.S. Food and Drug Administration." Premarket Notification 510(k). N.p., n.d. Web. 11 Nov. 2015. http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketnotification510k/default.htm

In order to be substantially equivalent to a legally marketed medical device, a device must have the same intended use as the predicate device and have the same technological characteristics as the predicate device. Different technical characteristics mean that there has been a significant change in the materials, design energy source, or other features (compared to the predicate device). If the device has different technical characteristics, the applicant must demonstrate that the device is as safe and effective as the predicate device.[85] If the FDA believes that there is insufficient evidence to establish substantial equivalence, it will request additional information. If such information does not result in substantial equivalence, a non-substantial equivalence determination (NSE) is made and the device will be treated as a class III device requiring a PMA.

The FDA on Substantial Equivalence:[86]

> •"For purposes of subparagraph (A), the term "different technological characteristics" means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device".
>
> •"In contrast, FDA generally evaluates differences between the new device and the predicate device to determine their effect on safety and effectiveness. It follows that the evidence necessary to show substantial equivalence will increase as differences between the new device and the predicate device increase if those differences significantly affect, or may significantly affect, safety or effectiveness (21 CFR 807.81)".
>
> •"For FDA to evaluate whether differences exist between the technological characteristics of the new device and the predicate device(s), the manufacturer should clearly identify the technological characteristics of each device individually. Technological characteristics include materials, design, energy source, and other device features, as defined in section 513(i)(1)(B) of the FD&C Act and 21 CFR 807.100(b)(2)(ii)(A)". A 510(k) submission must also contain information about the technological characteristics of the predicate device (21 CFR 807.87(f), 807.92(a)(3) and (a)(6)). FDA relies upon information provided about the predicate device, in addition to the

---

[85] The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notification. July 28, 2014 CDRH. FDA defines "Intended Use" as: The term "intended uses" refers to the objective intent of the persons legally responsible for the labeling of the device. The intent is determined by their expressions or may be shown by the circumstances surrounding the distribution of the device. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such representatives. It may be shown by the offering or the using of the device, with the knowledge of such persons or their representatives, for a purpose for which it is neither labeled nor advertised. The general statement of the "Indications for Use" identifies the target population in a significant portion of which sufficient valid scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device. The Indications for Use statement, as defined by the FDA, has a very defined structure. The Intended Use on the other hand is a regulatory term that describes an overall picture. https://alwaysincompliance.wordpress.com/2011/09/02/intended-use-vs-indications-for-use/

[86] The 510(k) Program: Evaluation Substantial Equivalence in Premarket Notifications. Guidance for Industry and Food and Drug Administration Staff. FDA Center for Devices and Radiologic Health.

> information in our files as appropriate, and the new device to determine whether the new device has different technological characteristics (Decision Point 3) in comparison to the predicate(s)".

On **September 23rd of 2003**, Ethicon's Senior Project Manager of Regulatory affairs emailed his associates at Ethicon a letter indicating that PROSIMA would not need FDA clearance for marketing:

> *"GYNECARE GYNEMESH PS is classified by the FDA as a class II device under regulations 878.3300 and as such is subject to a 510(k) Premarket Notification to the FDA. According to the FDA Guidelines, adding new sizes (or shapes) does not require a new 510(k). The line extension of the products offered will be documented."* [87]

This statement is not supported by the FDA Guidelines. The changing of sizes and shapes in this instance substantially altered the technical characteristics of the mesh. This alone would require a 510(k), in which Ethicon would need to demonstrate that such a change in technical characteristics did not affect the safety and efficacy of the device. Furthermore, the PROLIFT contained additional new components that had not been cleared by the FDA. Indeed, these findings were noted by the FDA, which informed Ethicon that PROLIFT contains "shaped mesh and specialized tools" and that the shapes "are significantly different than the previously cleared rectangle meshes. These new shapes have the potential to raise new questions of safety and effectiveness."[88]

In a letter dated **October 6th of 2004**, from Ethicon Senior Project Manager of Regulatory Affairs, Sean O'Bryan, to Ethicon's Director of Research and Development, Scott Ciarrocca, as well as its worldwide director of regulatory affairs and other colleagues, Mr. O'Bryan stated with regard to PROLIFT, "The Instruments are classified by the FDA as a Class I sterile surgical instruments and are exempt from premarket notification in accordance with 21 CFR parts 807.85 and 884" and "According to the completed Flowchart A and Flowchart B (See attached) relating to labeling changes and technology changes respectively, a new 510(k) is not required. The changes do not significantly affect the safety and effectiveness of the product."[89] Mr. O'Bryan adds:

> *"Finally. GYNECARE GYNEMESH PS and the instruments described above may be included as components in procedural kits as appropriate for its intended uses as described in 510(k) premarket notification K951476. ETHICON, Inc. certifies that all components of these kits are 1) exempt from premarket notification (consistent with the exemption criteria described in the classification regulations and the limitations of exemptions from Section 510(k) of the Act (21 CFR Section*

[87] ETH.10204

[88] ETH.MESH.00083765

[89] ETH.10206

807.85); 2) found to be substantially equivalent through the premarket notification process under the Food, Drug and Cosmetic Act for the use for which the kit is intended."

Mr. O'Bryan's statements are incorrect and do not represent the material facts:

- The instruments of PROLIFT had not been classified by the FDA as a class one device, were not exempted from the 510 (k) process. Indeed, a quick search of the FDA product classification database would have revealed that many surgical instruments, instruments that do not pierce blindly and sharply pass through the body, have been given class 2 designations (require a 510(k)). Examples of such class 2 instruments include Obstetric and Gynecologic devices, such as a uterine tenaculum (a simple clamp for grabbing the uterus), a vaginal dilator (a blunt form for stretching the vagina), a cervical cone knife (a scalpel for cutting the cervix), and a fibroid screw (a cork-screw type trocar for pulling on a fibroid). In addition, looking at laparoscopic accessories by way of example, 21 CFR part 884 (referenced by Mr. O'Bryan) states that certain accessories that are not part of delivery system may be assigned to class 1.[90] The FDA teaches:

    - Class I devices are deemed to be low risk and are therefore subject to the least regulatory controls. For example, dental floss is classified as Class I device.
    - Class II devices are higher risk devices than Class I and require greater regulatory controls to provide reasonable assurance of the device's safety and effectiveness. For example, condoms are classified as Class II devices.[91]

- Anyone skilled in the art could recognize that the PROLIFT accessories (guides with cannula and retrieval devices) are more invasive and more likely to cause harm than the class 2 instruments referenced above. Furthermore, the PROLIFT accessories are clearly part of a delivery system. The preponderance of the evidence suggests that the PROLIFT accessories are and were class 2, and required a 501 (k) submission.

- As discussed elsewhere in the monograph, the FDA makes clear the fact that any technical changes that affect safety and efficacy shall require a 510(k) submission. As noted by the FDA, the differences between GYNEMESH PS and the PROLIFT device represent technical changes that necessitated a 510(k).[92] Mr. O'Bryan was incorrect.

---

[90] Title 21--Food And Drugs Chapter I--Food And Drug Administration Department Of Health And Human Services Subchapter H--Medical Devices. Part 884 -- Obstetrical And Gynecological Devices Subpart B--Obstetrical and Gynecological Diagnostic Devices Sec. 884.1720 Gynecologic laparoscope and accessories.

[91] http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194438.htm

[92] ETH.MESH.00083769

- Mr. O'Bryan's statement that all components of the PROLIFT kit were exempt from premarket notification or shown to be substantially equivalent to legally marketed device/s was incorrect. As noted above, the accessories were not shown to be exempt. Furthermore, no component had yet been shown to be substantially equivalent (SE) to a legally marketed device. Ethicon had not undergone a pre-submission meeting with the FDA, nor otherwise solicited any opinion from the FDA with regard to SE. Indeed, several years later, the FDA would notify Ethicon that it would need to complete the 510(k) process and demonstrate SE.

In a letter to "customer," dated **February 8th of 2005**, Ethicon's PROLIFT Senior Project Manager (Regulatory Affairs) stated:

> "GYNECARE PROLIFT* Pelvic Floor Repair Systems is considered a line extension of the existing marketed GYNECARE GYNEMESH* PS device. GYNECARE GYNEMESH PS received 510(k) clearance on January 8, 2002 (K013718). According to the FDA Guidelines, GYNECARE PROLIFT is covered by this existing approval (see attached FDA Clearance Letter K013718).
>
> The Instruments are classified by the FDA as a Class I sterile surgical instruments and are exempt from premarket notification in accordance with 2 1 CER parts 807.85 and 884.[93]

In March of 2005, without clearance from the FDA, Ethicon began to market its PROLIFT device. There are no FDA guidelines that would provide that the marketing of the GYNEMESH PROLIFT device was covered by the previous clearance of one component of the device, the GYNEMESH PS. Indeed, this is substantiated by the fact that two years after the initial marketing of PROLIFT, upon becoming aware of PROLIFT, the FDA informed Ethicon that it could not market PROLIFT until it completed the it 510(k) process:

> ***"You may not market this device until you have provided adequate information described above and required by 21 CFR 807.87(1), and you have received a letter from the FDA allowing you to do so. If you market the device without conforming to those requirements, you will be in violation of the Federal Food, Drug, and Cosmetic Act".***[94]

On **May 21st of 2007**, Ethicon submitted to the FDA a Premarket Notification, 510(k), for its GYNECARE PROLIFT+M* Total, Anterior, and Posterior Pelvic Floor Repair Systems. This was a device was the same as its PROLIFT device, with the exception of the fact that the mesh had been changed. Ethicon had substituted its ULTRAPRO Mesh for its GYNEMESH, as secondary to what it described in its internal commercialization

[93] ETH.10208

[94] ETH.MESH.00083769

strategy document to be marketing needs: "To continue meeting market needs, Ethicon Women's Health & Urology knows it is critical to integrate a lighterweight pre-shaped synthetic mesh in the PROLIFT system in order to maintain market share. Looking at quickly available synthetic meshes within the Ethicon Products portfolio, ULTRAPRO product has been identified as the preferred choice because of its characteristics and lower density."[95] When Ethicon began marketing its PROLIFT device in 2005, it inappropriately bypassed the FDA PMA and 510(K) processes, as noted herein, with the justification that PROLIFT represented merely a shape change in GYNEMESH PS, a product already cleared for marketing for an indication that included treating "the pelvic floor in vaginal wall prolapse."[96] Unlike GYNEMESH PS, ULTRARO was not indicated for use in the pelvic floor in vaginal wall prolapse and was only cleared for use in repairing the abdominal wall. Ethicon's rationalization was to suggest it could market its GYNECARE PROLIFT +M without submitting to the FDA either a PMA, premarket approval application, or a 510(k) application. Ethicon opted for the 510(k) pathway, the pathway that required the least amount of safety and efficacy data.

In its 510 (k) application for PROLIFT +M, Ethicon claimed substantial equivalence to its own ULTRAPRO Mesh, GYNECARE GYNEMESH PS PROLENE Soft MESH, and GYNECARE PROLIFT Pelvic Floor Repair Systems. As noted elsewhere herein, predicate devices must be pre-amendment devices, approved by the PMA process, or cleared by the 510 (k) process. The GYNECARE PROLIFT Pelvic Floor Repair Systems met none of these requirements. Ethicon, possibly in anticipation of the fact that it was potentially making the FDA aware of this illegally marketed device, offered the FDA the following statement: "GYNECARE PROLIFT* Pelvic Floor Repair Systems (insignificant change - line extension of GYNECARE GYNEMESH PS*, ETHICON, Inc. K013718)." As the PROLIFT device had never been tested in animals or clinical trials, the only performance data Ethicon could provide was its original ULTRAPRO ISO 10993-1 and bench and cadaver data. The FDA recognized that PROLIFT had not been cleared for market and requested from Ethicon an explanation for its claim of "insignificant change" from its GYNEMESH PS device.

On **July 19th of 2007,** Ethicon responded to the FDA. Ethicon stated that that the only technical change was that of instruments and shape, and that "clinical data was not deemed necessary to exhibit safety and effectiveness for a shape change to an existing device plus kitting with inserter tools" and that "Design Validation did not raise new issues of safety and effectiveness of the mesh implant or inserter tools."[97] Based on such, Ethicon concluded its letter to the FDA by restating that PROLIFT represented an insignificant change from GYNEMESH PS and required only internal documentation. On **July 31st of 2007,** the FDA informed Ethicon that internal documentation would not suffice and, "at a minimum," Ethicon would need to submit and "add-to-file" containing:

---

[95] ETH-60382

[96] K013718. http://www.accessdata.fda.gov/cdrh_docs/pdf/k013718.pdf

[97] ETH.MESH.00011818

- The specific changes made to the device originally cleared under K013718
- A statement of whether or not these changes alter the safety and/or effectiveness of the product as compared to the device cleared under K03718
- Any and all relevant tests and data related to the performance of the new, altered device (in this case the Gynecare PROLIFT Repair system)[98]

On **August 10th of 2007,** the FDA notified Ethicon that they had reviewed the add-to-file document and that they had determined that the changes Ethicon made to GYNEMESH PS were significant and did indeed require a traditional 510(k). The FDA stated, however, that it would allow the PROLIFT SE data to be submitted as part of the PROLIFT +M 510(k) application.[99] The add-to-file data was addended to the PROLIFT +M 510(k) file, K071512.

On **August 27th of 2007,** the FDA informed Ethicon that it had reviewed the materials submitted for K071512.[100] In this correspondence, the FDA notified Ethicon of 16 deficiencies. On **September 20th of 2007,** Ethicon responded.[101]

> **Deficiency One**: The Gynecare PROLIFT + M Pelvic Floor Repair Systems (Total, Anterior, and Posterior) and the Gynecare PROLIFT Pelvic Floor Repair Systems (Total, Anterior, and Posterior) are devices that include a shaped mesh and specialized surgical tools. The PROLIFT + M Systems contain a mesh equivalent in chemical composition to ULTRAPRO Mesh (cleared, K033337). The PROLIFT Systems contain a mesh equivalent in chemical composition to PROLENE Soft Mesh (cleared, K013718). The meshes in both PROLIFT Systems are uniquely shaped and this design is supposed to accommodate the anatomy specific to the pelvic/urogenital region. These shapes are significantly different than previously cleared rectangular meshes. **These new shapes have the potential to raise new questions of safety and effectiveness given that surgical procedure using the PROLIFT Systems will not be equivalent to the surgical procedure for placement of the predicate devices. Please provide a rationale for substantial equivalence of the PROLIFT and PROLIFT + M Systems to your predicate devices.**
>
> The FDA herein points out that there are two significant changes that need to be addressed - the new mesh shapes and the new procedure for placing the new shapes. The FDA has requested the rational for claiming SE to the square pieces of mesh without instruments. As noted elsewhere herein, as there is clearly a change in technical characteristics, Ethicon must respond to this question by providing evidence that there is a change in safety or efficacy.

---

[98] ETH.10148

[99] ETH.10148

[100] Via email, ETH.10148 and later by mail, ETH.MESH .00083765

[101] ETH.00928

Ethicon's Response & (Expert Opinion on Response):

- "GYNEMESH PS is typically cut into shape similar to those of the preshaped PROLIFT and PROLIFT +M, and placed using inserter tools similar to those provided with the PROLIFT and PROLIFT+M systems."
    - (Prior to the marketing of the PROLIFT device, there were no tools similar to those provided with the PROLIFT and PROLIFT +M devices. Ethicon itself provides a lengthy disclosure to the USPTO in which it describes the novelty of its tools. The USPTO agreed that PROLIFT tools were unique and in May of 2009 granted Ethicon a patent on these tools.)
    - (Although it is certainly possible that a small number of Ethicon's paid consultants, including the inventor of the PROLIFT, were cutting GYNEMESH into experimental shapes similar to those of PROLIFT, GYNEMESH PS was not "typically" cut into shapes similar to that of PROLIFT. As discussed elsewhere herein, during the Ethicon sponsored GYNEMESH PS device validation, the six key opinion leader urogynecologists each cut a different shape, none of which was the size or shape of PROLIFT. I have trained over 1000 surgeons and, to this day, have not met a surgeon (other than several paid Ethicon consultants), that cut GYNEMESH PS or any other mesh into a mesh with arms).

      (The response to this deficiency is both incorrect and deceitful.)

- "The inserter tools that are included in the PROLIFT and PROLIFT+M" systems, if sold separately, would all be Class I devices, as summarized in the table below":

DEVICE	CLASSIFICATION	PRODUCT CODE	REGULATION
Guide	Class I	GDF	§878.4800
Cannula	Class I	GEA	§878.4800
Retrieval Device	Class I	GAE	§878.4800

    - (The Code of Federal Regulations section referenced in this table is for GENERAL AND PLASTIC SURGERY DEVICES, Manual surgical instruments for general use. The 3 part PROLIFT tool is not only dissimilar to examples provided in this section of the CFR, but this cited CFR section stipulates "A surgical instrument that has specialized uses in a specific medical specialty is classified in separate regulations in parts 868 through 892." The PROLIFT surgical instruments are quite specialized, not for general or plastic surgery, and for a very complicated gynecologic surgery. Indeed, part 884, OBSTETRICAL AND GYNECOLOGIC DEVICES, section 884.4530, is for Obstetric-Gynecologic specialized manual instruments. The majority of

examples offered by the FDA within this section have been designated as Class 2 devices, devices that require a 510(k)).

(The response to this deficiency is both incorrect and deceitful.)

- "For placement of the devices, substantial equivalence was demonstrated through cadaver modeling and animal lab testing. Neither cadaver models, nor animal testing raised any new issues of safety and effectiveness of the meshes that are the subject of this response".
- Ethicon offers additional predicate devices. "However, additional TVM systems currently on the market, such as AMS Apogee Vault Suspension System (K040537) and AMS Perigee System (K040623), require "blind" insertion procedures for the treatment of pelvic organ and vaginal wall prolapse. ETHICON has shown that the PROLIFT and PROLIFT+M Systems are substantially equivalent to currently marketed AMS Apogee and Perigee systems, based on shape, insertion procedure, and performance characteristics. Thus, ETHICON has amended the substantial equivalence section of the 510(k) that is the subject of this response to include the AMS devices listed above. The following procedural outlines are taken from the AMS website (www.americanmedicalsystems.com) and both require "blind" passage of surgical instruments in the vaginal wall, similar to the PROLIFT and PROLIFT+M systems. The complete Instructions for Use for the Apogee and Perigee Systems can be found on pages 79-94 of Attachment IV."

Deficiency Two: In the Clinical Evaluation section of your submission, you state "The performance of the system is further supported with a clinical series conducted at two centers. These results are not yet published, but the authors have submitted a manuscript for publication that is summarized in the Clinical investigations section of this document." However, in the next section titled "Clinical investigations" you state that "No clinical investigations have been conducted on the use of Gynecare PROLIFT Pelvic Floor Repair System." Please clarify whether any clinical studies have been performed using the Gynecare PROLIFT and Gynecare PROLIFT+M Systems. If clinical studies have been conducted with either or both of your proposed devices, please provide a complete report which details the study protocol, collected data, data analyses, and conclusions.

The FDA here points out that the clinical studies submitted by Ethicon were admittedly not performed with the PROLIFT device. The FDA here is requesting a complete and detailed report of clinical studies utilizing the PROLIFT and PROLIFT +M devices.

Ethicon's Response & (Expert Opinion on Response):

- "Post-market clinical evaluations were performed using the GYNEMESH* PS (K01371 S), with the purpose of evaluating the GYNEMESH for anterior, posterior and vault prolapse repair using the TVM technique. These samples were provided pre-cut, in shapes similar to the GYNECARE PROLIFT system with a single, simple insertion instrument, but were not provided with a complete set of inserter tools. Therefore, no clinical investigations were conducted on the use of GYNECARE PROLIFT Pelvic Floor Repair System. Although we do not feel that clinical studies are necessary to demonstrate substantial equivalence, we have included the TVM internal study reports in Attachment V of this response.
    - (Ethicon here admits that it had been marketing the PROLIFT device without clinical data on the PROLIFT device. Ethicon provides that it did initiate post-market clinical evaluation with pieces of GYNEMESH PS that were cut "similar" to PROLIFT. However, the tools of PROLIFT were not yet included. Ethicon herein tells the FDA that they "do not feel that clinical studies are necessary to demonstrate equivalence." However, as already discussed in this monograph, the technical characteristics of PROLIFT and PROLIFT +M are quite different than GYNEMESH, ULTRAPRO, and the AMS products. The mesh shape, tools of insertion, method of insertion, and anatomy traversed by the armed mesh are unique. Hence, bench and cadaver testing clinical studies cannot demonstrate safety and efficacy and clinical studies are absolutely necessary. Furthermore, the FDA had already stipulated that "due to the complexity" of the procedure, bench testing would not be sufficient to demonstrate device safety and efficacy and clinical evaluation would be necessary.[102])
    - (Ethicon failed to disclose that its investigators performing the referenced internal TVM study had already published concerning data on TVM (**2005**). Over 12% of patients undergoing the TVM procedure (invented by Jacquetin and assigned to Ethicon) had experienced vaginal mesh exposure within 2 months of implantation and the majority required surgical intervention.[103] These Ethicon-paid investigators concluded "Nowadays, based on these data, we can only advise that caution be exercised when carrying out this new surgical procedure. In fact, experimental studies and clinical trials seem necessary in order to reduce the level of exposure to less than 5% of cases.")

---

[102] ETH.00932

[103] Collinet, Pierre, Franck Belot, Philippe Debodinance, Edouard Ha Duc, Jean-Philippe Lucot, and Michel Cosson. "Transvaginal Mesh Technique for Pelvic Organ Prolapse Repair: Mesh Exposure Management and Risk Factors." .International Urogynecology Journal Int Urogynecol J. 17.4 (2005): 315-20.

- (Ethicon failed to disclose that the one-year analysis of its French TVM study (8 of the 11 centers referenced by Ethicon). The PROLIFT device had failed to meet its success criteria. 18.4% of patients had met the surgical failure criteria at one year (CI interval reached 26.6%).[104] Of additional concern, the investigators noted a 12.6% incidence of moderate to severe vaginal contraction. The final version of this report as completed on **June 27, 2006**.)
- (Ethicon also failed to disclose that its investigators performing the referenced internal TVM study were in possession of concerning data, based on the evaluation of almost 700 patients that had undergone the TVM procedure.[105] The investigators had found an almost 18% incidence of vaginal contraction associated with the armed anterior TVM. The investigators found that retraction was significantly linked to recurrent prolapse (p=.007). The investigators concluded that "[T]he present study shows a relatively high incidence of late post-surgical complications" and "It appeared that direct suspension of the posterior mesh with the sacrospinous suspension increases the rate of symptomatic retraction of the mesh and therefore we should try to avoid direct tension of vaginal meshes." The findings of this study would be submitted for publication in **January of 2008,** well in advance of the February of 2008 Ethicon letter to the FDA.[106])

  (The response to this deficiency failed to disclose critical material facts and is both incorrect and deceitful.)

- "No clinical evaluations have been performed on the GYNECARE PROLIFT+M system. As PROLIFT+M is a Class II device (Product Code: FTL), demonstrating substantial equivalence to the predicate devices has been done with pre-clinical bench top testing, and additional cadaver testing. This type of testing has been sufficient to demonstrate substantial equivalence for the identified predicates devices."
  - Ethicon herein admits that no clinical testing had been done for PROLIFT +M. Ethicon suggests that bench and cadaver testing have shown PROLIFT +M to be SE to the claimed predicate devices. However, as already discussed in this monograph, the technical characteristics of PROLIFT and PROLIFT +M are quite different than GYNEMESH, ULTRAPRO, and the AMS products.

---

[104] ETH.MESH.00012009

[105] Caquant, Fréderic, Pierre Collinet, Philippe Debodinance, Juan Berrocal, Olivier Garbin, Claude Rosenthal, Henri Clave, Richard Villet, Bernard Jacquetin, and Michel Cosson. "Safety of Trans Vaginal Mesh Procedure: Retrospective Study of 684 Patients." Journal of Obstetrics and Gynaecology Research 34.4 (2008): 449-56.

[106] ETH-01748

The mesh shape, tools of insertion, method of insertion, and anatomy traversed by the armed mesh are unique. Hence, bench and cadaver testing clinical studies cannot demonstrate safety and efficacy and clinical studies are absolutely necessary.)

(The response to this deficiency failed to disclose critical material facts and is both incorrect and deceitful.)

Expert Opinion on deviation from medical and or industry standards #1:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature, as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and scientific certainty that:

- Surgeons implanting a medical device expect a device to have been clinically tested on the target patient population and proved safe and effective prior to marketing,
- Medical device companies are typically aware of the fact that surgeons implanting a medical device expect a device to have been clinically tested on the target patient population and proved safe and effective prior to marketing, and that
- Ethicon knowingly opted to not perform such clinical testing and not inform surgeons that it had not performed such testing.
- I can say to a reasonable degree of medical certainty that many surgeons would not have implanted PROLIFT if they had been informed of these facts.

Further:

- The majority of surgeons rely on medical device companies as their primary or sole source of data with regard to safety and efficacy,
- Surgeons expect the safety and efficacy data provided by device companies to be complete, concise, and in no way misleading,
- Medical device companies are aware that many surgeons rely on them as the primary and or sole source of safety and efficacy data,
- Medical device companies are aware of industry standards in labeling, including the use of non-ambiguous language and the inclusion of all important material facts, and
- Medical device companies are aware that the failure to provide such information in its labeling places patients at substantial risk of harm.
- I state with a reasonable degree of medical certainty, based on my knowledge, training, and experience, that Ethicon knowingly deviated from medical and industry standards by opting to withhold meaning

material facts and data from the PROLIFT labels and that such behavior resulted in patient harm.

Deficiency Three: One of the publications cited in your submission (Altman D and Falconer C. *Perioperative Morbidity Using Transvaginal Mesh in Pelvic Organ Prolapse Repair*. Obstetrics & Gynecology 2007; 109 (2, Part 1): 303-308) concludes with the following cautionary remarks regarding the use of biomaterials in pelvic surgery:

"Compared with suburethral tapes, biomaterials used at pelvic organ prolapse repair increase the biomaterial load considerably because of the increased size of the mesh. This may increase the risk for adverse tissue reactions and biomaterial-associated complications. Although the polypropylene compound used for TVT and transvaginal mesh is identical, other characteristics, such as elasticity and pore size, differ. One should, therefore, not assume that the biomaterial properties are the same for the two procedures, and results from incontinence surgery may not be directly applicable to pelvic organ prolapse surgery."

"Given this conclusion, please justify your conclusion that clinical evaluation of the meshes included in the Proift +M and PROLIFT Systems is not necessary."

Ethicon's Response & (Expert Opinion on the Response):

- "Biocompatibility testing has been conducted on both the PROLENE material found in GYNEMESH* PS (K013718) (used in PROLIFT) and the ULTRAPRO mesh (K033337) (used in PROLIFT+M) with the results indicating that the meshes are appropriate for long-term implantation per the ISO 10993 standard."
    - (As discussed elsewhere in this monograph, polypropylene degrades following implantation. ISO 10993 requirements require prolonged biocompatibility testing for implants that degrade, ISO 10993-6. This section of 10993 stipulates that local tissue responses should be evaluated relative to the degradation process of the implant at various time points: where there is no or minimal degradation, usually to be evaluated at 1 week to 12 weeks after implantation; when degradation is taking place; or when a steady state has been reached resulting in tissue restoration or degradation nearing completion. The guideline provides for evaluations for up to two years post-implantation. Ethicon did not perform the ISO 10993 testing required for its degrading implant, GYNEMESH PS.)
    - (Ethicon failed to disclose that its biocompatibility testing, completed in 2001, had demonstrated numerous concerning characteristics of GYNEMESH PS.[107] Some of these concerns were

[107] ETH.MESH.01217931. An Exploratory 91-Day Tissue Reaction Study Of Polypropylene-Based Surgical Mesh In Rats

published in 2006.[108] This 91 day study, a study that implanted different mesh types into the back of rats, found that GYNEMESH PS inflammation was not significantly decreasing at 91 day, there was a unique loss of connective tissue associated with the implantation of GYNEMESH PS, and 60% of the cases of GYNEMESH implantation were associated with adherence to the underlying muscle, a finding not observed with other meshes.[109])

- "All implanted materials have associated risks, which are normally disclosed in the labeling. The package inserts for both PROLIFT and PROLIFT+M state that "potential adverse reactions are those typically associated with surgically implantable materials, including...inflammation..."""
    - (Anyone familiar with product labeling would agree that risks "are normally disclosed in the labeling." However, as discussed elsewhere in this monograph, the risks of GYNEMESH PS are not typically associated with surgically implanted material, but rather are associated with unique risks and unique incidences of risks. Both this response and the referenced label are misleading. The response neither addresses the deficiency noted by the FDA, nor in any way responds to the associated request to "justify your conclusion that clinical evaluation of the meshes included in the Prolift +M and PROLIFT Systems is not necessary.")
- "For those cases where an adequate surgical repair is not possible without additional supporting or bridging material, the risks associated with mesh implants have been deemed to be appropriate, given the benefit they provide, as traditional POP repairs have a failure rate that ranges between 25% and 52%."
    - (Once again, this response neither addresses the deficiency noted by the FDA, nor in any way responds to the associated request to "justify your conclusion that clinical evaluation of the meshes included in the Prolift +M and PROLIFT Systems is not necessary." This statement does, however, indicate that PROLIFT is indicated for the patients in whom surgical repair is not possible without additional supporting or bridging material. However, Ethicon does neither teaches in its labeling or elsewhere that the PROLIFT device should be limited to this unique patient population, nor teaches a means of identifying this unique patient population. In stark contrast to this, Ethicon teaches in its patient label that "[P]rocedures with the GYNECARE PROLIFT are appropriate for most patients."[110] Ethicon further indicates that the risks are deemed appropriate

[108] Barbolt, Thomas A. "Biology of Polypropylene/polyglactin 910 Grafts." International Urogynecology Journal Int Urogynecology 17.S1 (2006): 26-30.

[109] ETH.MESH.01217931

[110] ETH.01797

in this population, yet offers no supporting evidence for this statement. Although the range of surgical failure cited for traditional POP repairs is erroneous and inflated, it is worth noting that Ethicon's TVM study had already disclosed a 1-year failure rate that fell into this same range. Ethicon failed to disclose this fact.)

(The response to this deficiency failed to disclose critical material facts and is both incorrect and deceitful.)

Expert Opinion on deviation from medical and or industry standards #2:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony, and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect that the manufacturer has performed appropriate and complete biocompatibility testing prior to the marketing of a surgical implant,
- Surgeons expect to be informed if the risk/benefit ratio is only appropriate to a small subset of the disorder cohort, and that
- Device manufacturers are aware that surgeons expect that appropriate and complete biocompatibility testing has been performed prior to the marketing of a surgical implant.
- Ethicon knowingly did not perform such testing.
- Ethicon knowingly did not inform surgeons of the fact that it believed the surgery was indicated for a unique subset of the disorder cohort, a small and poorly defined group of women with POP.
- These deliberate omissions resulted in patient injury.

Deficiency Four: Recently, both the FDA Office of Surveillance and Biometrics and the Office of Compliance have received complaints related to use of your meshes sold under the Gynecare family of products. Additionally, a Manufacturer and User Facility Device Experience (MAUDE) Database search of Medical Device Reports (MDRs) limited to brand names ETHICON TVT and ETHICON GYNEMESH for the period of August 2004 to August 2007 has returned a significant number of reported adverse events.

For the Gynecare GYNEMESH device, 174 reports describe patients experiencing adverse events such as mesh erosion and extrusion, infection and abscess, perforations of internal organs, bleeding and hematoma, and incontinence. The majority of patients required readmission to the hospital for

additional surgery, such as removal of a portion or the whole mesh, lysis of adhesions, antibiotic therapy, and blood transfusions.

It is possible that additional adverse events were missed during this search, due to the many brand names (for the same mesh composition and intended use) under which the ETHICON meshes are sold.

The mesh included in the Gynecare PROLIFT System is identical in composition and intended use to these two devices mentioned above. Please provide a discussion of how the Gynecare PROLIFT System can be used safely and effectively, taking into account these reported adverse events.

Ethicon's Response & (Expert Opinion on Response):

- "All implanted materials have associated risks, which are normally disclosed in the device labeling. For those cases where an adequate surgical repair is not possible without additional supporting or bridging material, the risks associated with mesh implants have been deemed to be appropriate given the benefit they provide".
    - (As discussed in my opinion on Ethicon's response to deficiency number 3, GYNEMESH and PROLIFT, as discussed in detail previously, have unique risks, and there are no data to support the statement that the "risks associated with mesh implants have been deemed to be appropriate given the benefit they provide." This statement is not true when applied to either the general prolapse population or this small, poorly defined subset of patients described by Ethicon. Indeed, even today, eight years later, there is no data to support this statement. To the contrary, the systematic review of the literature has failed to demonstrate a quality of life advantage associated with the use of TVM.)
- "In response to this inquiry, the company compared adverse event rates for GYNEMESH to those for PROLIFT since PROLIFT differs only in that it is pre-cut for surgeon convenience and provides in a kit the surgical tools the physician will use for insertion. PROLIFT was originally released to the market based on regulatory coverage via the GYNEMESH 5I0(k) (K0137I 8) and data was gathered independent of GYNEMESH. As is seen in the comparison table below, the rate of adverse reactions reported (# reported /sales) is comparable between the two versions of the device. As shown, the event rates are small percentages of device sales. In 2005, the events for GYNEMESH PS were prospectively collected in the TVM clinical study, which explains the higher percentage in comparison to 2006-2007."

"In addition, MDR rates were evaluated for GYNEMESH and PROLIFT from 2005 to 2007. The MDR rates for each year are again comparable for GYNEMESH and PROLIFT. As shown, the MDR rates are small percentages of device sales. In 2005, the MDRs for GYNEMESH PS were prospectively collected in the TVM clinical study, which explains the higher percentage in comparison to 2006-2007."[111]

GYNEMESH PS			
	MDR'S	SALES	MDR RATE %
2005	59	9907	0.60
2006	14	6865	0.20
2007 YTD	9	4665	0.19

PROLIFT			
	MDR'S	SALES	MDR RATE %
2005	12	6284	0.19
2006	43	15375	0.28
2007 YTD	39	12994	0.30

- (The FDA had already informed Ethicon that the differences between GYNEMESH PS and PROLIFT were significant and that GYNEMESH PS is not a sufficient predicate device to PROLIFT. As previously described in this monograph, the technical characteristics are different; therefore, safety and efficacy must be demonstrated. The FDA here states its concern about the high number of MDR reports for GYNEMESH PS. Based on the concerning number of GYNEMESH PS complications and the fact that GYNEMESH PS is part of the PROLIFT device, the FDA has asked for Ethicon to discuss how PROLIFT can be used safely. In its response, Ethicon states that the MDRs for the PROLIFT device are Comparable to the MDRs of the GYNEMESH PS device. This does not equate to a discussion of how PROLIFT can be used safely.

  In addition, Ethicon tabulated the MDRs for GYNEMESH and PROLIFT and compared MDRs as a percentage of sales (not total implants). Although it is an accepted fact that the MDR complication rates represent only a small fraction of actual complications, trends of MDR complication rates should follow trends in actual complication rates. The tabular reports provided by Ethicon show that GYNEMESH PS complications trended downward between 2005 and 2007, whereas PROLIFT complications trended upward. In addition, in 2007, reported MDR rates as a percentage of sales were higher for PROLIFT than GYNEMESH. Although Ethicon indicates a 2007 PROLIFT MDR

[111] Table supplied by Ethicon as part of its response to this deficiency.

rate (based on sales not implants) of less than 1%, it does not disclose that investigators in its TVM study had already published a report demonstrating a 33.6% late complication rate, a 10% erosion rate, a 12.7% rate of severe to moderate vaginal contraction, or a 4.5% incidence of hematoma. Its investigators had concluded that PROLIFT was associated with a high incidence of late post-surgical complications.[112]

Ethicon's discussion does not provide any reassurance that the GYNEMESH PS containing PROLIFT will be safer than GYNEMESH PS. Ethicon only provides evidence that complications are more common with PROLIFT. Ethicon does not reveal critical, material facts with regard to known and concerning PROLIFT complication rates. Ethicon provides misleading information with regard to the risk-benefit ratio for a unique and poorly defined patient population.)

(This response to this deficiency failed to disclose critical material facts, is both incorrect and deceitful, and is not responsive the FDA request to describe "how the Gynecare PROLIFT System can be used safely and effectively, taking into account these reported adverse events.)

Expert Opinion on deviation from medical and or industry standards #3:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect to be informed of the degree of difficulty or surgical skill required to use a medical device,
- A manufacturer must inform users if the use of its device is complex and requires a skilled user,
- Surgeons implanting a medical device expect a device to have been clinically tested on the target patient population and proven safe and effective prior to marketing,

---

[112] Caquant, Fréderic, Pierre Collinet, Philippe Debodinance, Juan Berrocal, Olivier Garbin, Claude Rosenthal, Henri Clave, Richard Villet, Bernard Jacquetin, and Michel Cosson. "Safety of Trans Vaginal Mesh Procedure: Retrospective Study of 684 Patients." .Journal of Obstetrics and Gynaecology Research</i> 34.4 (2008): 449-56. Collinet, Pierre, Franck Belot, Philippe Debodinance, Edouard Ha Duc, Jean-Philippe Lucot, and Michel Cosson. "Transvaginal Mesh Technique for Pelvic Organ Prolapse Repair: Mesh Exposure Management and Risk Factors." .International Urogynecology Journal Int Urogynecol J</i> 17.4 (2005): 315-20. ETH.MESH.00012009

- Medical device companies are typically aware of the fact that surgeons implanting a medical device expect a device to have been clinically tested on the target patient population and proven safe and effective prior to marketing.
- Ethicon knowingly opted to not inform surgeons that its product was intended for skilled surgeons, knowingly opted not to perform clinical testing, and knowingly opted not to inform surgeons that it had not performed such testing.
- I can say to a reasonable degree of medical certainty that many surgeons would not have implanted PROLIFT, if they had been informed of these facts.

Deficiency Five: The deficiencies noted above highlight potential issues with the safety and efficacy of the Gynecare PROLIFT System. In addition, the sketches provided in the Design Validation Report of the Amendment show complex placement of your mesh within a very complex anatomical location. This complex procedure is proposed to be done in a "blind" manner through the use of the specialized surgical tools provided in the Gynecare System. Due to the complexity of this procedure and potential high risk for organ perforation, bench testing is not sufficient to demonstrate device safety and efficacy. Please provide a clinical evaluation of your proposed PROLIFT System to support your Indications for Use.

Ethicon's Response & (Expert Opinion on Response):

- "Placement of any surgical device, regardless of the manner of placement, has the potential to result in patient injury associated with the procedure or the device. The shape of the GYNECARE PROLIFT System was designed in response to the needs of skilled surgeons who treat pelvic organ prolapse and are familiar with the anatomy of the region. In addition, the shapes of the GYNECARE PROLIFT and PROLIFT+M Systems are similar to currently marketed AMS Apogee and AMS Perigee Systems, as per diagrams/photos below. All systems listed provide a surgical mesh body with arms for tension-free placement." [113]

[113] Image shown below text is included in Ethicon's response to this deficiency.

Figure 1: PROPOSED: GYNECARE PROLIFT Pelvic Floor Repair Systems – GYNEMESH PS Mesh Implant

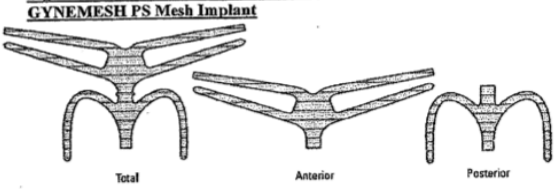


Figure 2: PROPOSED: GYNECARE PROLIFT+M Pelvic Floor Repair Systems – GYNEMESH M Mesh Implant (A=Total, B=Anterior, C=Posterior)

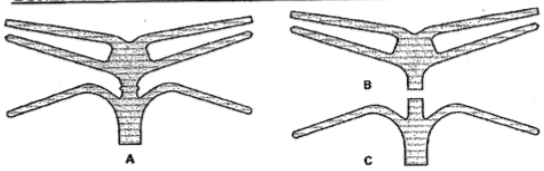
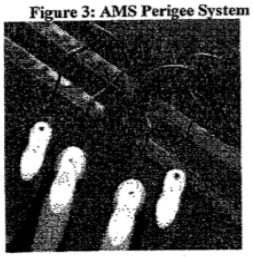
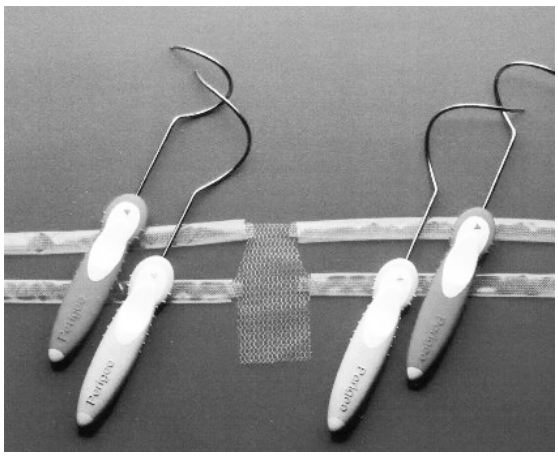


Figure 3: AMS Perigee System (K040623) (Anterior Mesh ONLY with inserter tools)



- (The FDA herein requested that Ethicon provide a clinical evaluation of the PROLIFT System to support its Indication for Use. The Indication for Use did not include a restriction to "skilled surgeons" who "are familiar with the anatomy of the region." The shapes of the PROLIFT and AMS implants were not similar and the devices differed in numerous ways. The angles of the arms were quite different and, as described by the inventor of PROLIFT, such angles may affect the rectum.[114] Additionally, the arms of the AMS devices were sheathed, potentially decreasing bacterial contamination of the mesh arms. Furthermore, the AMS devices utilized a less complex set of tools and required less manipulation affecting neuromuscular and vascular spaces. Finally, the instruments associated with the anterior implants were of very different shapes. See comparative images of devices below (FIGURES 2, 3, and 4). Ethicon provides no information that is responsive to the FDA request for "a clinical evaluation of your proposed PROLIFT System to support your Indications for Use."

[114] US 7,131,944 B2



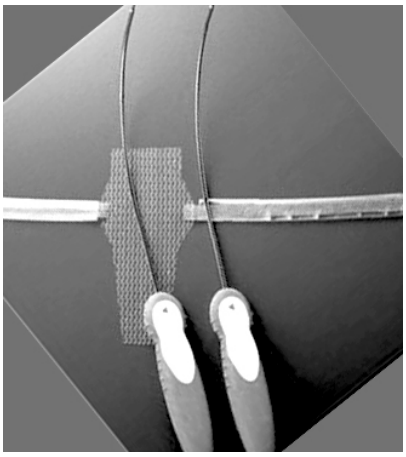


FIGURE 2
AMS ANTERIOR (PERIGEE) DEVICE[115] AMS POSTERIOR (APOGEE) DEVICE[116]

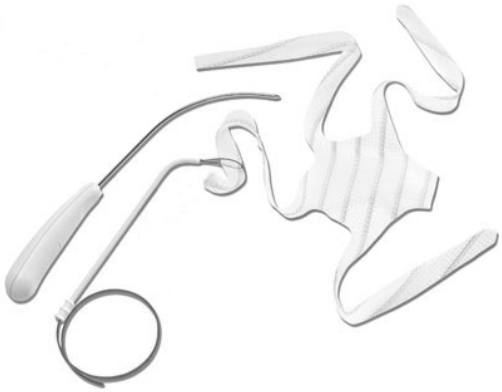


FIGURE 3
PROLIFT ANTERIOR[117]

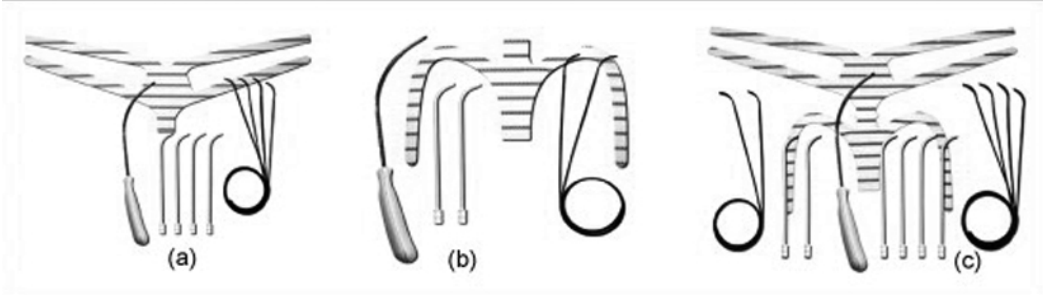


FIGURE 4
PROLIFT ANTERIOR, POSTERIOR, ANT TOTAL[118]

115 http://www.uromedperu.com/
116 http://www.obex.co.nz/Product/Index/337
117 http://www.kvadramed.ru/materials/gynecare/5.html

- "Although the Design Validation report exhibits a mesh placement that may appear complex, the knowledge and dissection of these spaces are part of a gynecologist's training. Therefore, the anatomical region is not considered "complex" to a trained gynecologist."
    - (To this day, over eight years since the initial and non-cleared marketing of the PROLIFT device, the requisite knowledge and dissection awareness of the spaces traversed by the blind PROLIFT through which the tool passes and other important aspects of mesh implantations are not part of either general gynecologic or urologic training programs. The PROLIFT procedure requires the blind passage of its novel tools and novel mesh shapes through the adductor space of the leg, the obturator externus and internus muscle, and the para-rectal and anal spaces above and below the levator ani muscle group. For this reason, to this day, there are few to no gynecologist or urologists willing to try to explant the PROLIFT arms from these spaces. Ethicon's paid PROLFIT expert recently disclosed in her expert opinion that, although "the large mesh with 8 arms looked ominous," by "the second year of fellowship (Urogynecology fellowship), I was very comfortable."[119])

- "For the GYNECARE PROLIFT System, cadaver modeling and Design Validation presented no issues of safety and efficacy in relation to user interface with the device."
    - (The FDA had already advised that bench testing is not sufficient to demonstrate device safety and efficacy and instructed Ethicon to provide clinical evaluation in support of the PROLIFT Indications for Use. The cadaver modeling and design validation do not represent a clinical evaluation. Indeed, in the next paragraph in its response, Ethicon states that its testing is "pre-clinical.")

- "ETHICON believes that the results of pre-clinical, benchtop testing, and cadaver evaluations, provide evidence of substantial equivalence of the PROLIFT Systems to the currently marketed GYNEMESH and demonstrate that surgeons can use the device without problems."
    - (The FDA had already warned Ethicon that "due to the complexity of this procedure and potential high risk for organ perforation, bench testing is not sufficient to demonstrate device safety and efficacy" and instructed

---

[118] Ouzaid, I., J.-F. Hermieu, V. Misraï, P.-N. Gosseine, V. Ravery, and V. Delmas. "Traitement Du Prolapsus Génital Par Renfort Transvaginal Prolift® : Une étude Prospective." Progrès En Urologie 20.8 (2010): 578-83.

[119] Expert report of Joye K. Lowman, M.D., MPH, the case of Patricia L. Hammons, Plaintiff, v. Ethicon, Inc., et al., Defendants. Philadelphia County Court. May Term 2013. No. 3913

Ethicon to provide "clinical," not "pre-clinical" evaluation. Furthermore, the FDA had already informed Ethicon that the GYNEMESH PS is not a sufficient predicate. Finally, benchtop testing and cadaver modeling cannot "demonstrate that a surgeon can use the device without problems.")

(The response to this deficiency failed to disclose critical material facts, is both incorrect and deceitful, and is not responsive the FDA request to provide a clinical evaluation of the proposed PROLIFT System to support its Indications for Use.)

Expert Opinion on deviation from medical and or industry standards #4:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect to be informed of the degree of difficulty or surgical skill required to use a medical device,
- A manufacturer must inform users if the use of its device is complex and requires a skilled user,
- Surgeons implanting a medical device expect a device to have been clinically tested on the target patient population and proved safe and effective prior to marketing,
- Medical device companies are typically aware of the fact that surgeons implanting a medical device expect a device to have been clinically tested on the target patient population and proved safe and effective prior to marketing.
- Ethicon knowingly opted to not inform surgeons that its product was intended for skilled surgeons, knowingly opted not to perform clinical testing, and knowingly opted not to inform surgeons that it had not performed such testing.
- I can say to a reasonable degree of medical certainty that many surgeons would not have implanted PROLIFT if they had been informed of these facts.

Deficiency Six: The Gynecare PROLIFT+M System includes a mesh identical to the ULTRAPRO Mesh. The ULTRAPRO Mesh is a knitted mesh composed of an absorbable poliglecaprone-25 and nonabsorbable polypropylene. Please describe if the poliglecaprone and polypropylene fibers are twined together to form a Single fiber that is then knitted to form a mesh or if the poliglecaprone

fibers are knitted together with polypropylene fibers. Please describe the mesh structure that remains after the poliglecaprone original mesh has degraded in vivo. Specifically, is the overall mesh structure retained with thinner/fewer fibers when only the polypropylene fibers remain.

Ethicon's Response & (Expert Opinion on Response):

- "One poliglecaprone thread with a diameter of 5 mils and one polypropylene thread with a diameter of 3.5 mils are twisted together to form a single fiber that is knitted to form a mesh. The polypropylene fibers that remain maintain a diameter of 3.5mils. Burst strength testing has been performed on the "naked" (i.e. post-absorbed) ULTRAPRO mesh (found in PROLIFT+M mesh) to demonstrate substantial equivalence to the predicate PROLENE Soft Mesh. Pore size also remains the same. See page 49 of the original Premarket Notification submission for testing results.
    - (The FDA specifically asked for a description of the mesh *in vivo* following degradation of the poliglecaprone. Ethicon's response on pore size is a physical impossibility. Investigators have demonstrated that the heavier GYNEMESH undergoes a complete loss of porosity under a load of only 4.9N/cm. This is much less than the load associated with maximum abdominal pressure.)[120]

      (Ethicon is responsive to the question; however, its response is misleading.)

Expert Opinion on deviation from medical and or industry standards #5:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons implanting a medical device that will undergo rapid and significant partial absorption expect that the post absorption device to have been clinically tested on the target patient population and proved safe and effective prior to marketing,

[120] Otto J, Kaldenhoff E, Kirschner- Hermanns R, Muhl T, Klinge U. Elongation of textile pelvic floor implants under load is related to complete loss of effective porosity, thereby favoring incorporation in scar plates. J Biomed Mater Res A 2014;102:1079-84. Barone W, Moalli P, Abramowitch S. Vari- able porosity of common prolapse meshes during uni-axial loading. Female Pelvic Med Reconstr Surg 2013;19(Suppl 2):S56.

- Medical device companies are typically aware of the fact that surgeons implanting a medical device expect a device to have been clinically tested, in its expected state, on the target patient population and proved safe and effective prior to marketing, and
- Ethicon knowingly opted to not perform such clinical testing and not inform surgeons that it had not performed such testing.
- I can say to a reasonable degree of medical certainty that many surgeons would not have implanted PROLIFT if they had been informed of these facts.

Deficiency Seven: As stated above, the PROLIFT+M System mesh is partially absorbable. In addition, the predicate device, ULTRAPRO Mesh, is intended for use in hernia repair, which is significantly different in anatomical location and pathology than pelvic floor and vaginal wall prolapse repair. The biocompatibility, bench performance, and animal testing that you have provided for the ULTRAPRO Mesh is not sufficient to support the use of a partially absorbable mesh for pelvic floor and vaginal wall prolapse repair. The tests provided also do not support the successful use of the PROLIFT+M System for a complicated surgical procedure and placement of this device. Please provide a clinical evaluation of your proposed PROLIFT +M System to support your proposed Indications for Use.

Here, the FDA is instructing Ethicon that its claimed predicate mesh has a different intended use and that biocompatibility testing, bench testing, and animal testing will not be sufficient to demonstrate safety and efficacy for the proposed new Indication for Use, a complicated prolapse surgery. The FDA instructs Ethicon to provide a clinical evaluation for the PROLIFT+M device to support its proposed Indication for Use.

Ethicon's Response & (Expert Opinion on Response):

- "ETHICON believes that the testing provided in the PROLIFT+M Premarket Notification is sufficient to demonstrate substantial equivalence of the PROLIFT+M mesh to the currently marketed ULTRAPRO Mesh. We have demonstrated that ULTRAPRO Mesh and GYNEMESH provide substantially equivalent and adequate strength for repair of hernia and pelvic organ prolapse, respectively. The revised predicate comparison/substantial equivalence table can be found in Attachment I of this supplemental submission."
    - (Attachment I provides only bench testing. The FDA instructed Ethicon that, secondary to the proposed new Indication for Use and the complexity of this use, biocompatibility testing, bench testing, and animal testing will not be sufficient to demonstrate safety and efficacy.)

- "Historically, the least burdensome approach to demonstrating substantial equivalence of a mesh indicated for hernia repair (PROLENE Soft Mesh, K001122) to a mesh indicated for pelvic floor repair (GYNEMESH, KO 13718) has included comparative bench data on the mesh itself, biocompatibility assessment per the ISO standards, and animal/cadaver testing demonstrating that no new issues of safety or efficacy are raised. This is consistent with the Surgical Mesh guidance provided by FDA, "Guidance for the Preparation of a Premarket Notification Application for Surgical Mesh."

  "For PROLIFT+M, the company utilized the approach outlined above. The mesh in the PROLIFT+M system (a.k.a. GYNEMESH M) is identical in material and structure to ULTRAPRO Mesh. Bench testing of the ULTRAPRO Mesh device followed FDA's Guidance Document, "Guidance for the Preparation of a Premarket Notification Application for Surgical Mesh." This bench testing demonstrates that the mesh material for PROLIFT+M provides the equivalent mechanical characteristics as the GYNEMESH PS and ULTRAPRO mesh [PLEASE CONFIRM], and is therefore substantially equivalent. Therefore, ETHICON believes that utilizing existing bench performance data animal testing, and biocompatibility results from ULTRAPRO Mesh is appropriate to support a pelvic floor indication for PROLIFT+M."

  "In the case of biocompatibility data, testing for ULTRAPRO mesh in a hernia application is considered to represent the biocompatibility of PROLIFT+M mesh in the pelvic organ prolapse application, as PROLIFT+M is identical in material and structure to ULTRAPRO mesh. The testing performed per ISO 10993-1 on ULTRAPRO mesh is identical to the testing that would have been performed for the PROLIFT+M mesh. Although the anatomical location from hernia repair to pelvic floor repair differs, the fascial tissue in the abdomen is comparable to that in the pelvis. Upon placement of PROLIFT+M mesh, the straps will provide tension placement to allow for tissue integration into the mesh."

  - (The FDA instructed Ethicon that, secondary to the proposed new Indication for Use and the complexity of this use, biocompatibility testing, bench testing, and animal testing will not be sufficient to demonstrate safety and efficacy. Furthermore, the failure to comply with ISO 10993-6 is even more significant for ULTRAPRO than it is for GYNEMESH PS. With this mesh, there will be two separate timelines for degradation, one for poliglecaprone-25 and one for polypropylene. Ethicon incorrectly states that the fascial

tissues of the abdomen are comparable to those in the pelvis. The fascia of the pelvis is non-uniform and complex in nature. They are derived from coalescence of both visceral and parietal peritoneums and have been described as being composed of three levels and having numerous areas of densification, such as the cardinal ligaments, uterosacral ligaments, the arcus tendineus facial pelvis, the arcus tendineus levator ani, and pericervical ring. Furthermore, the fascial of the pelvis surrounds and supports the rectum, bladder, and vagina and mesh related inflammation, contraction, and erosion have much graver consequences than when such occur on the fascia of the abdomen.)

- "After tissue integration, the non-absorbable polypropylene mesh structure will continue to provide support to the pelvic floor. Mouritsen, et al., concluded in their paper with regard to "[v]aginal pressure during daily activities before and after vaginal repair," that intra-vaginal pressures are highest during coughing and Valsalva." The mean vaginal pressure experienced during these activities was less than 1.42 psi (100 cm HTO) in all cases. ULTRAPRO Mesh has been shown through benchtop burst testing to exhibit 90 psi (6,327.6 cm H2O) after absorption (see page 49 of the original submission)."
    - (The FDA instructed Ethicon that, secondary to the proposed new Indication for Use and the complexity of this use, biocompatibility testing, bench testing, and animal testing will not be sufficient to demonstrate safety and efficacy. The FDA instructed Ethicon to provide a clinical evaluation for the PROLIFT+M device to support its proposed Indication for Use. Furthermore, the bench testing of burst strength tells us little about the *in vivo* strength following degradation of the polypropylene component of ULTRAPRO.)

- "In addition, the cadaver evaluation of PROLIFT+M resulted in successful placement of the device using four evaluating surgeons. The GYNECARE PROLIFT device, similar in shape and placement to PROLIFT+M, also demonstrates successful placement in Design Validation and cadaver studies. To corroborate the GYNECARE PROLIFT data, results of the TVM clinical evaluation in both France and US do not present issues of safety and efficacy. Although the French study did not meet the criteria for success, the study did demonstrate reasonable success rates compared to the 30% re-operation rate using traditional vaginal prolapse repair. Although ETHICON does not believe that clinical studies are necessary to demonstrate substantial equivalence, we have included the TVM internal study reports to in Attachment V of this response."

- (Successful placement of PROLIFT+M in a cadaver by 4 expert key opinion leaders is not sufficient clinical evidence of safety and efficacy for the proposed Indication for Use. The FDA later points out that similar cadaveric evaluation of PROLIFT by non-experts demonstrated errors, including loss of instrument location within the body and damage to mesh insertion instrumentation.[121] In addition, as already noted, many of the TVM investigators had already published concerning data with regard to safety.[122] Although Ethicon does not provide a citation for the 30% traditional surgery re-operation rate, re-operation rates have been reported to be as low a zero at one year.[123] More importantly, in January of 2008, a group of TVM investigators had already reported an 18% re-operation rate of 3.6 months.)[124]

- "ETHICON believes that with the evidence provided in the original Premarket Notification submission, GYNECARE PROLIFT+M is substantially equivalent to currently marketed ULTRAPRO mesh."
  - (Substantial equivalence requires the same intended use and the same technical characteristics. The FDA already stated that the Indication for Use is different. Furthermore, the technical characteristics of GYNEMESH PROLIFT+M and ULTRAPRO are different as the shape and design are different and ULTRAPRO does not include the novel instrumentation of PROLIFT+M. In recognition of these facts, the FDA is instructing Ethicon that its bench testing, animal testing, and cadaver modeling were insufficient to demonstrate safety and efficacy (an necessary component of SE determination) and that it must provide clinical evaluation to support safety and efficacy. Ethicon never provided such.)

    (The response to this deficiency failed to disclose critical material facts, is both incorrect and deceitful, and is not responsive to the FDA request to provide a clinical

---

121 See Deficiency number 11

122 Caquant, Fréderic, Pierre Collinet, Philippe Debodinance, Juan Berrocal, Olivier Garbin, Claude Rosenthal, Henri Clave, Richard Villet, Bernard Jacquetin, and Michel Cosson. "Safety of Trans Vaginal Mesh Procedure: Retrospective Study of 684 Patients." .Journal of Obstetrics and Gynaecology Research</i> 34.4 (2008): 449-56. Collinet, Pierre, Franck Belot, Philippe Debodinance, Edouard Ha Duc, Jean-Philippe Lucot, and Michel Cosson. "Transvaginal Mesh Technique for Pelvic Organ Prolapse Repair: Mesh Exposure Management and Risk Factors." .International Urogynecology Journal Int Urogynecol J</i>

123 Chmielewski L, Walters MD, Weber AM, et al. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol 2011;205:69.e1-8

124 Caquant, Fréderic, Pierre Collinet, Philippe Debodinance, Juan Berrocal, Olivier Garbin, Claude Rosenthal, Henri Clave, Richard Villet, Bernard Jacquetin, and Michel Cosson. "Safety of Trans Vaginal Mesh Procedure: Retrospective Study of 684 Patients." .Journal of Obstetrics and Gynaecology Research</i> 34.4 (2008): 449-56.

evaluation of the proposed PROLIFT+M System to support its Indications for Use.)

Expert Opinion on deviation from medical and or industry standards #6:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons implanting a medical device expect a device to have been clinically tested on the target patient population and proven safe and effective prior to marketing,
- Medical device companies are typically aware of the fact that surgeons implanting a medical device expect a device to have been clinically tested on the target patient population and proved safe and effective prior to marketing, and
- Ethicon knowingly opted to not perform such clinical testing and not inform surgeons that it had not performed such testing.
- I can say to a reasonable degree of medical certainty that many surgeons would not have implanted PROLIFT if they had been informed of these facts.

Deficiency Eight. The device description given for your Gynecare PROLIFT and Gynecare PROLIFT+M Systems does not adequately describe the dimensions of the meshes. Please provide detailed dimensions for the shaped mesh, including lengths and widths of the straps and area of the central body.

Ethicon's Response & (Expert Opinion on Response):

- "Please see Attachment III of this response for dimensions of the anterior, posterior, and total systems."
    - (There is no drawing to accompany the measurements provided in Attachment III. This is necessary to provide meaning to the measurements. This document does not provide the information necessary to assist a surgeon in determining what percentage of the mesh is remaining following an attempted removal. By way of example, following several years of the marketing of PROLIFT, Ethicon introduced its new POP mesh kit, PROSIMA. Figure 5, provided in the PROSIMA IFU, provides a drawing with

measurements.[125] This may assist the surgeon at time of attempted explantation.)

(The response to this deficiency is incomplete and neither completely addresses the request of the FDA, nor provides the surgeon with information requisite to mitigate surgical complications.)

Expert Opinion on deviation from medical and or industry standards #7:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons implanting a medical device need to know the dimensions of the device and a surgeon cannot safely and consistently remove a fragile implant without knowing the dimensions of the implant. Ethicon knowingly excluded such information from its label and this resulted in patient injury.

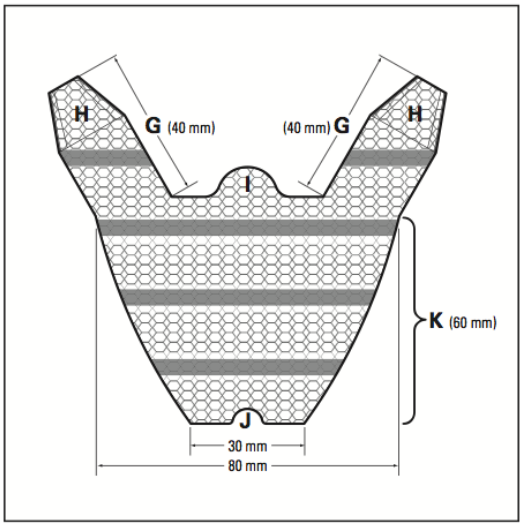


FIGURE 5

Deficiency Nine: You have not provided any new mechanical testing performed on the mesh included in the Gynecare PROLIFT+M System. Instead, you have provided the mechanical testing of the predicate device, ULTRAPRO

[125] Gynecare PROSIMA. P21070/d. STATUS:02/2010. Copyright Ethicon 2008.

Mesh, which has the identical chemical composition to your proposed device. However, you state that the proposed mesh is identical to the ULTRAPRO Mesh except for the addition of a mesh relaxation operation and laser cutting. The mesh relaxation and laser cutting may have significant effects on the mechanical properties of your device. Please provide test reports for mechanical testing performed on your proposed device. Please beware that mechanical testing for this device should include the general performance tests applicable to rectangular meshes as well as specific to the shape of these proposed meshes.

Ethicon's Response & (Expert Opinion on Response):

- "Test reports exhibiting the performance of the relaxed and laser-cut mesh compared to non-relaxed, non-laser-cut mesh will be available mid-October."

Deficiency Ten: Mechanical testing of the Gynecare PROLIFT System was not provided in the Amendment to this 5I0(k). Please provide test reports for mechanical testing performed on the Gynecare PROLIFT System.

Ethicon's Response & (Expert Opinion on Response):

- Mechanical testing of the mesh for GYNECARE PROLIFT was obtained from the GYNECARE GYNEMESH Premarket Notification (KO13718). Please see the predicate comparison/substantial equivalence table (Attachment1) for details. However, as GYNEMESH is mechanically cut, whereas GYNECARE PROLIFT is laser-cut, additional data will be available mid-October, addressing the change in device characteristics with the laser-cutting process step.

Deficiency Eleven: The physicians who evaluated the Gynecare PROLIFT System surgical procedure in a cadaver were not experienced users of the PROLIFT System. The physicians who evaluated the Gynecare PROLIFT+M System surgical procedure in a cadaver were experienced users of the PROLIFT System. There were obvious usage differences between inexperienced and experienced physicians. For example, errors such as organ perforation and loss of instrument location within the body occurred with inexperienced users. Therefore, it is plausible to conclude that the Gynecare Systems require significant experience, in order to have surgical success. Please provide a description of surgical training that will be required to learn how to use your Gynecare Systems. Please also include the duration and intensity of training that will be required prior to surgical attempt in a patient, in order to have a successful surgery with minimal errors with the physician's first patient.

Ethicon's Response & (Expert Opinion on Response):

- "Although some usage differences exist between inexperienced and experienced users of the PROLIFT Systems, the cadaver labs did not result in organ perforation or loss of instrument location within the body, as stated above. Deviations in the GYNECARE PROLIFT Design Validation report, provided in Appendix VIII of the Add-to-File document, indicate some usage issues associated with the device, including:

  - Recognized perforation of the cannula sidewall with the guide. Note that the cannula sidewall is not an anatomical structure, but rather is a portion of the insertion tool.
  - Cannula tip gets "lost" in deep tissue. This statement indicated that the surgeon had difficulty tactilely feeling the tip of the cannula during use, not that a portion of the device is left behind during insertion.

  These Design Validation comments were noted but determined to be "minor inconveniences" to the surgeon rather than any sort of safety or efficacy issue. Also, it was noted that with the usage of PROLIFT by inexperienced surgeons, no issues occurred during Design Validation or cadaver labs that would have resulted in patient injury."
    - (Ethicon is not correct in stating that damage to the cannula by non-experienced users is not a "minor inconvenience." Any damage to the cannula can cause tearing, fraying, or other damage to the mesh arms with resultant injury, pain syndromes, or device failure. Ethicon is also not correct in stating that the inability of the non-experienced user to feel (locate) the sharp tip of the PROLIFT guide as it passes blindly trough the body near organs and vital nerves and blood vessels is a "minor inconvenience." The potential severe complications are obvious to anyone skilled in medicine and or anatomy. Damage to the cannula and an inability to locate the sharp tip of the guide represent significant issues that effect both safety and efficacy.)

- "The instructions for Use for GYNECARE PROLIFT and PROLIFT+M Systems state "Training on the use of the [systems] is recommended and available. Contact your company sales representative to arrange for this training." ETHICON offers the following types of training:

- Preceptorships – The preceptee learns procedure via didactic presentation and observation of 3-4 surgeries at the preceptor's hospital.
- Proctorships – The preceptee learns the procedure via didactic presentation and the preceptor "walks them through" the procedure at the preceptee's hospital.
- Cadaverlab- Anatomic, cadaver training and didactic presentation on the procedure and placement of the device."

- (Although the FDA specifically asked for a description of the surgical training required, Ethicon herein provides only that training is available, not required. Although the FDA specifically asks for a description of the duration and intensity of surgical training required prior to attempting to implant PROLIFT in a patient, Ethicon does not provide such information. It should, however, be noted that the duration of such training events is typically one day and preceptees receive no hands-on live human training "prior to surgical attempt in a patient," the index event of concern to the FDA.)

  (The response to this deficiency is both incorrect and deceitful, and is not responsive to the FDA request to provide the duration and intensity of training required prior to performing the PROLIFT procedure in a patient.)

Expert Opinion on deviation from medical and or industry standards #8:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- (The inability to identify the sharp tip of a tool passing through the body near vital organs, nerves, and blood vessels is not a "minor inconvenience," indeed, this is both a safety and efficacy concern, and an increased risk amongst inexperienced users due to an inability to identify the sharp tip of a tool is something users expect to find and be alerted to in a label. Ethicon knowingly deviated from medical and industry standards by opting to excluded such information from its label and this resulted in patient injury.)

Deficiency Twelve. The labeling for the Gynecare PROLIFT+M Systems was reviewed and the following items were found to be deficient. Please address these issues and provide revised labeling for your proposed device.

- The percent loss of strength (in vivo) of the mesh as the poliglecaprone component is absorbed should be included in your Instructions for Use under the performance section.

Ethicon's Response & (Expert Opinion on Response):

- "ULTRAPRO Mesh (K033337), the currently marketed predicate and identical material to PROLIFT+M mesh, does not address percent loss of strength of the mesh in its Instructions for Use. Therefore, ETHICON does not believe that such a statement should be required to be included in the PROLIFT Systems IFU.

  The percent loss of burst strength from pre-absorption (135 psi) to post-absorption (90 psi) is approximately 33%. However, this value is relatively meaningless and potentially confusing to the surgeon, as the purpose of the absorbable component is to aid in intraoperative handling and placement of the mesh. The company has demonstrated that the strength of the non-absorbable mesh portion greatly exceeds the forces experienced in situ."

  - (Although the FDA instructed Ethicon to add the "percentage of loss of PROLIFT+M strength "in vivo" to the labeling of the device, Ethicon stated that is should not have to add this information, as it was not required for the ULTRAPRO Mesh, a proposed predicate with a different Indication for Use. Ethicon makes the unsubstantiated claim that loss of strength is "relatively meaningless" and that the company had demonstrated that the post-absorption strength exceeds the forces experienced *in situ*. As discussed elsewhere in this monograph, the company never evaluated, as requested here by the FDA, the post-absorption burst strength "in vivo" (the burst strength following implantation with resultant degradation of the polypropylene component). Ethicon only tested the burst strength of its mechanically cut ULTRAPRO mesh cut following removal of the absorbable poliglecaprone-25 fiber.[126] This mesh was not tested after in vivo absorption and in vivo degradation of the polypropylene component. Furthermore, as pointed out by the FDA in Deficiency Nine, the PROLIFT+M is different than the ULTRAPRO, it has been laser cut and put through a process of "mechanical relaxation." In its response to Deficiency Nine, Ethicon

[126] ETH.01065

made it clear that it never did testing to support a claim for any percentage of in vivo strength loss of GYNEMESH PS.)

- You have not provided sufficient evidence to support the statement "the bi-directional elastic property allows adaptation to various stresses encountered in the body." Although you have shown that bi-axial anisotropy exists in tensile properties of your mesh that is dependent on the direction of knitting machine axis, it is unlikely that this anisotropic mechanical property will be able to accommodate for physiological stresses encountered in a multi-axial anisotropy environment within the body. You have also not demonstrated that your mesh is elastic. Please either remove this statement from your Instructions for Use or provide in vivo experimental evidence that your mesh has elastic properties that allows adaptation to physiological stresses.

Ethicon's Response & (Expert Opinion on Response):

- We agree that sufficient evidence has not been provided to make this statement. We have removed the statement from the IFU.
  - **(Ethicon here admits that it has been in violation of a federal law. Ethicon admits to the misbranding of its PROLIFT device in its Instructions for Use Label.)**

Deficiency Thirteen. The Amendment was originally submitted as an add-to-file, which was later, converted to a 510(k) submission and included as an amendment to this 510(k) submission. Due to this 510(k) conversion, there are several essential items required for a 510(k) submission that are missing, such as labeling. Please provide the device labeling and other essential items necessary for a 510(k) submission for your Gynecare PROLIFT System.

Ethicon's Response & (Expert Opinion on Response):

- "Please see Attachment IV of this response for the updated 510(k) submission".
  - **(Ethicon had not previously submitted its labeling to the FDA. Hence, any and all misbranding represents over 2 years of violations of federal laws on misbranding).**

Deficiency Fourteen: The Amendment included in this 510(k) describes a device (Gynecare PROLIFT System) that is different than the Gynecare PROLIFT+M System proposed in the original submission. Due to the addition of the Gynecare PROLIFT System for review in this submission, the original Indications for Use, 510(k) Summary, and Truthful and Accurate Statement provided are not applicable. Please provide a revised Indications for Use,

510(k) Summary, and Truthful and Accurate Statement that reflects both of the Gynecare System devices currently under review.

Ethicon's Response:

- "Please see Attachment IV of this response for the updated 510(k) submission".

Deficiency Fifteen: The 510(k) Summary that is provided does not provide an adequate description of material components and the performance tests used to evaluate your proposed device. Please provide a more detailed and comprehensive description of material components and performance testing in your revised 510(k) Summary.

Ethicon's Response:

- "Please see Attachment IV of this response for the updated 510(k) submission".

Deficiency Sixteen: In your submission, you have several names that refer to your proposed devices, ranging from Lightning mesh to GYNEMESH M. With the addition of the amendment which describes another device with a very similar name, the PROLIFT System, it has become difficult to distinguish between the different mesh types and may affect the review of your submission. Please be sure to clearly identify each of your proposed and predicate meshes with distinguishing names in your response to these deficiencies.

Ethicon's Response:

- "Please see Attachment IV of this response for the updated 510(k) submission."

On **January 3rd of 2008,** the FDA electronically notified Ethicon of seven additional deficiencies. On **February 21st of 2008,** Ethicon submitted its responses to these deficiencies.[127]

Deficiency One: In your original 510(k) submission, dated May 31, 2007, you referenced a "... clinical series conducted at two centers. The results are not yet published, but the authors have submitted a manuscript for publication that is summarized in the Clinical Investigations section of this document." In this Supplement, you have clarified that more than two centers participated in this study, and you have provided a copy of the manuscript titled "Clinical Assessment of Feasibility, Complications and Effectiveness at Twelve Months,

[127] ETH-01236

Three Years and Five Years of the TVM Technique for Genital Prolapse." In this series, the investigators placed Gynecare GYNEMESH PS (Nonabsorbable Soft Mesh) in anterior and posterior repair of pelvic organ prolapse into the vagina. Gynecare GYNEMESH is made from the same material as Gynecare PROLIFT; therefore FDA believes that the results of this clinical study are relevant to Gynecare PROLIFT. (Gynecare GYNEMESH is different material however compared to PROLIFT + M making the study less useful for the purposes of providing performance data to support clearance of PROLIFT + M).

In view of the serious nature of Medical Device Reports associated with A/P vaginal wall repairs using Gynecare GYNEMESH received by FDA, it is important to include a summary of the above clinical data in labeling for Gynecare PROLIFT. We request that you include a summary of this clinical data and provide the revised labeling for review. We have prepared the following summary of the clinical data for the study cohort in France for your consideration. You may use the summary for the French cohort and also as a template for preparing a summary of the US cohort. If the study subjects are able to be pooled, you may wish to provide a single summary for both cohorts.

"Clinical Performance Data"

As of December 2007, no prospective, controlled clinical trials have been conducted to evaluate the safety and effectiveness of Gynecare PROLIFT as mechanical support or bridging material of the fascial defect in repair of vaginal wall prolapse. Limited data are available from a prospective, non-randomized, non-controlled observational study using Gynecare GYNEMESH, a surgical mesh made of the same non-absorbable polypropylene as Gynecare PROLIFT. In the clinical study, the mesh was provided in pre-cut configurations however the insertion tools provided in the Gynecare PROLIFT kits were not available.

Inclusion Criteria

- Symptomatic prolapse of at least ICS Stage III
- 21 years or greater
- Does not wish future childbearing
- Uterus not retained
- Absence of uncontrolled diabetes
- No coagulation abnormality

Primary Endpoint

Proportion of subjects in whom correction of prolapse was achieved (ICS Stage 0 or 1) at 12-months post-operatively

Secondary Endpoints

- Prolapse in area not treated

- Peri-operative complications
- Subject tolerance of mesh
- Post-operative complications
- Quality of Life

Study Population
Ninety subjects were enrolled at eight centers in France. Eighty- seven were available for evaluation at 12-months post-pop. Demographics of this population are listed below:

Median age 66.5 (39.0-89.0) Median BMI 25.2 (17.9, 36.8) Prior vaginal delivery 96.7% Smoker within last five years 8%

Study Results
Effectiveness:
The study did not meet the pre-defined criteria of correction of prolapse of less than 20% (upper limit of 90% confidence interval). The observed rate of prolapse at 12-months was 18.4% (90% CI of 11.9-26.6).

PSI scores for vaginal prolapse improved from baseline (13.9, SD 5.7) to 12-months (1.9, SD 2.5). There was a trend to improvement of activities of daily living scores from baseline to 12-months post-operatively.

Safety:
Moderate/severe vaginal retraction (12%)
Visible or visible and palpable mesh exposure (10%) Surgical intervention for mesh exposure (6%)

Urinary tract infection within 6 weeks post-op (17%) Hematoma (5%)
Abscess (1%)
Vesicovaginal fistula (1%)

Ethicon's Response and (Expert Opinion on Response):

- "We have updated the IFU for the GYNECARE PROLIFT device to reflect the Trans-Vaginal Mesh clinical investigational data. We have modified the clinical summary to include data from both the French and US TVM studies and have also modified the formatting to save space, as this information will have to be translated into 28 languages within the IFU. The text to be incorporated is as follows:

  Clinical Performance Data

  Randomized, controlled clinical evaluations of GYNECARE PROLIFT System are underway, but at this time preliminary data are available

from two early observational studies of transvaginal mesh that were initiated in 2004. These observational studies evaluated a pre-cut surgical mesh made of the same non-absorbable polypropylene as the mesh used in GYNECARE PROLIFT System. For these studies, the mesh was provided in shape similar to that of the GYNECARE PROLIFT System, though implantation instruments were not provided in these studies. One of the two studies involved eight investigational centers in France; the second included three investigational centers in the US. The protocols were similar, where both studies were conducted to evaluate the usability of a pre-cut mesh for anterior, posterior, and vault prolapse in women with symptomatic prolapse of at least ICS Stage III using the precut mesh and a transvaginal surgical technique.

The inclusion criteria for both studies were as follows: symptomatic prolapse of at least ICS Stage III, subjects at least 21 years of age, subjects do not wish to become pregnant in the future, no uncontrolled diabetes, and no coagulation disorder. In the French study, an additional inclusion criterion was a prior or concurrent hysterectomy. The primary effectiveness endpoint for both studies was the proportion of subjects for whom correction of prolapse was achieved (ICS Stage 0 or I) evaluated at 12 months post-operatively. Secondary endpoints for both studies included: vaginal prolapse occurring in the area not treated with mesh, peri-operative complications, patient tolerance of synthetic mesh, post-operative complications, and quality of life (QOL). An additional secondary endpoint for the US study was the recurrence rate of vaginal prolapse in the area treated with mesh. Study populations available for follow-up at 12 months were 83 patients in the US and 87 patients in France with a median patient age of 62 and 66.5, respectively.

The 12-month postoperative study results were as follows (US, France): proportion of subjects with ICS Stage II or greater (12.0%, 18.4%), met pre-defined criteria of upper limit of 90% CI less than 20% (yes, no), Prolapse Symptom Index (PSI) mean (6.6, 3.1), Mean QOL score (0.7, 0.4).

Adverse events, expressed as percentages, were as follows (US, France): hematoma (3.5, 4.5), abscess (0, 1.1), urinary tract infection within 6 weeks post-procedure (8.2, 16.9), mesh exposure (14.1, 10.0), surgical intervention for mesh exposure (7.1, 5.6), vesico-vaginal fistula (1.2, 1.1), recto vaginal fistula (1.0, 0), moderate/severe vaginal retraction (3.6, 12.6).

More recent data specific to the GYNECARE PROLIFT System may be available in the published literature. Please contact your sales representative for more information.

Please refer to Attachment I for the updated GYNECARE PROLIFT System IFU."

- (The FDA indicated that secondary to the serious nature of the Medical Device Reports associated with A/P vaginal wall repairs using Gynecare GYNEMESH received by FDA, it was important for Ethicon to provide a summary of the Ethicon ongoing TVM studies in the PROLIFT labeling. The FDA went as far as to provide Ethicon with a template of such for the French TVM data and provided that Ethicon may use such summary as is and also use it as a template for the creation of a summary of the U.S. TVM data. The FDA, in accordance with its own labeling guidance, provided language that was clear, void of ambiguity, did not mislead, and did not leave out any important material facts. Ethicon chose not to use the templated language and made substitutions:

	FDA TEMPLATE LANGUAGE	ETHICON SUBSTITUTION FOR FDA LANAGUAGE
A	Limited data are available from a prospective, non-randomized, non-controlled observational study using Gynecare GYNEMESH, a surgical mesh made of the same non-absorbable polypropylene as Gynecare PROLIFT. In the clinical study, the mesh was provided in pre-cut configurations however the insertion tools provided in the Gynecare PROLIFT kits were not available.	[P]reliminary data are available from two early observational studies of transvaginal mesh. These observational studies evaluated a pre-cut surgical mesh made of the same non-absorbable polypropylene as the mesh used in GYNECARE PROLIFT System, though implantation instruments were not provided in these studies.
B	The protocols were similar, where both studies were conducted to evaluate the usability of a pre-cut mesh for anterior, posterior, and vault prolapse in women with symptomatic prolapse of at least ICS Stage III using the precut mesh and a transvaginal surgical technique.	The protocols were similar, where both studies were conducted to evaluate the usability of a pre-cut mesh for anterior, posterior, and vault prolapse in women with symptomatic prolapse of at least ICS Stage III using the precut mesh and a transvaginal surgical technique.
C	Effectiveness: The study did not meet the pre-	The 12-month postoperative study results were as follows (US,

C	Effectiveness: The study did not meet the pre-defined criteria of correction of prolapse of less than 20% (upper limit of 90% confidence interval). The observed rate of prolapse at 12-months was 18.4% (90% CI of 11.9-26.6).	The 12-month postoperative study results were as follows (US, France): proportion of subjects with ICS Stage II or greater (12.0%, 18.4%), met pre-defined criteria of upper limit of 90% CI less than 20% (yes, no).
D	Visible or visible and palpable mesh exposure (10%) Surgical intervention for mesh exposure (6%).	[M]esh exposure (14.1, 10.0), surgical intervention for mesh exposure (7.1, 5.6).

A. The FDA language draws attention to the fact the study was not prospective, randomized, or controlled. **The substituted language does not state that there was no cohort (comparison group) and assumes the reader will glean this from the limited data.**

B. The FDA template was based on the French study that included patients with stage 3 or greater POP. The substituted language of Ethicon refers to both the U.S. and the French studies. The U.S. study included patients with the less severe stage 2 POP.[128] **Ethicon here misleads the user to believe that the data from the U.S. study did not include the milder stage 2 POP. This is misbranding and misbranding is a violation of the law.**

C. The FDA language makes it obvious that the French study failed to meet the criteria for s surgical correction at 12 months. The substituted language provided by Ethicon does not make it clear that the French study failed to meet its success criteria. Instead of stating that it "did not meet" a success criteria, Ethicon offers a % that "met" an "upper limit" CI. Not only is it no longer clear that there was a failure to achieve a success criterion, but it is now easy to miss the fact that the French study failed in any way. **The substituted language of Ethicon is misleading and fails to disclose important material facts. This is misbranding and misbranding is a violation of the law.**

D. Although the rate of intervention for mesh extrusion is consistently reported between the FDA template and the Ethicon language, it is reported in an effectively misleading fashion. "Surgical intervention for mesh exposure of 7.1%" can mean that only 7.1% of subjects with mesh exposure required surgical intervention. However, more than 50% of patients with mesh extrusion required surgical intervention.[129] The percentages of surgical intervention for mesh extrusion reported by Ethicon herein most likely represent the percentage of total study

[128] ETH.MESH.00012109

[129] ETH.MESH.00012013 AND ETH.MESH.00012094

subjects undergoing surgical intervention for mesh extrusion, rather than the percentage of study subjects with exposure who needed intervention. **Ethicon's reporting of this percentage is effectively misleading and creates a false impression that only 5.6 to 7.1 percent of mesh extrusions will need surgical intervention. However, more than half will need surgical intervention. This is misbranding and misbranding is a violation of the law.)**

Expert Opinion on deviation from medical and or industry and or standards #9:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- The majority of surgeons rely on medical device companies as their primary or sole source of data with regard to safety and efficacy,
- Surgeons expect the safety and efficacy data provided by device companies to be complete, concise, and in no way misleading,
- Medical device companies are aware that many surgeons rely on them as the primary and or sole source of safety and efficacy data,
- Medical device companies are aware of industry standards in labeling, including the use of non-ambiguous language and the inclusion of all important material facts, and
- Medical device companies are aware that the failure to provide such information in its labeling places patients at substantial risk of harm.
- I state with a reasonable degree of medical certainty, based on my knowledge, training, and experience, that Ethicon knowingly deviated from medical and industry standards by opting to use misleading data in a misleading narrative and that such behavior resulted in patient harm.

Deficiency Two: The draft instructions for use for the PROLIFT and PROLIFT + M Pelvic Floor Systems do not adequately address issues of usability and potential adverse events. The following request for labeling revisions has taken into consideration data reported in the Trans-Vaginal Mesh placement clinical evaluations (both European and U. S. cohorts) that you have submitted, analysis of adverse events reported to the FDA for the PROLIFT device, and conclusions from publications specifically addressing PROLIFT device use. Please make the following labeling changes and submit revised labeling reflecting that these changes have been made.

a. In your instructions for use, the contraindications, warnings, precautions, adverse reactions, performance, sterility, disposal, and storage sections should be placed before the section illustrating the recommended surgical technique.

Ethicon Response (to a): The updated Instructions for Use for the GYNECARE PROLIFT and GYNECARE PROLIFT + M Pelvic Floor Systems, Attachments II, & I reflect the above change. The contraindications, warnings, precautions, and adverse reactions, performance, sterility, disposal, and storage all appear before the recommended surgical technique. However, based on clinician input, we believe that the description of the device should remain before the performance, sterility, disposal, and storage sections of the IFU.

b. All indications, contraindications, warnings, precautions, adverse reactions should be written prominent text as compared to the rest of the instructions for use.

Ethicon Response (to b): The updated IFU's, Attachment I & II, reflect the above change.

c. Following the statement "CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician," please add "Physicians should be trained in use of surgical mesh for treatment of pelvic organ prolapse and in management of complication resulting from such procedures."

Ethicon Response (to c): In our conference call on 1/22/08, we agreed to incorporate language regarding management of complications from mesh implantation into our existing statement. We have incorporated the following statement: “Training on the use of the GYNECARE PROLIFT + M* Pelvic Floor Repair Systems is recommended and available. The training is similar to the procedure using the GYNECARE PROLIFT* Pelvic Floor Repair System. Contact your company sales representative to arrange for this training. Physicians should have experience in management of complications resulting from procedures using surgical mesh. A similar statement appears in the GYNECARE PROLIFT IFU. We have updated the IFU’s, Attachments I & II, to reflect the above change.”

(The FDA has opined numerous times as demonstrated in the narrative of deficiencies that it feels that the PROLIFT device and procedures are complex and potentially unsafe. They have instructed Ethicon to instruct users that they should be trained in the management of complications. Ethicon has omitted this important information. Ethicon references a previous call with the FDA and suggests that the FDA agreed that this important teaching could be omitted from the label. However, such is not the case. In the referenced call, Ethicon stated that the placement of such language “will put ETHICON at a

disadvantage from competitive devices." The FDA did not respond by stating that the language could be omitted. The FDA rather stated that it would provide similar enforcement to the competitors: "this IFU information will be enforced for devices of this nature in the future" and "across the board." **By definition, an IFU must provide necessary instruction such that the user can use the device safely and for the purposes for which it is intended.[130] The omission of this required language creates an inadequate IFU. An IFU that is not adequate is a form of misbranding.[131] Misbranding is a violation of the law.**)

Expert Opinion on deviation from medical and or industry and or standards #10:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect to be informed and trained on unique device related complications, medical device companies are aware that they are the entity responsible for ensuring safety and efficacy,
- Medical device companies do not expect state or federal agencies to provide a warranty of safety and efficacy,
- Industry standards dictate that safety and efficacy should be monitored by internal policies and procedures, and that the failure to implement such policies places patients at substantial risk of substantial harm.
- I state with a reasonable degree of medical certainty, based on my knowledge, training, and experience, that Ethicon knowingly deviated from medical and industry standards when it opted to withhold safety related language from its label and that such resulted in injuries to patients.

Deficiencies and responses continued:

d. Please add, immediately above your indications statement, the statement "The safety and effectiveness of synthetic mesh or film support in transvaginal surgical procedures to treat pelvic organ prolapse have not been demonstrated in prospective, randomized clinical trials."

---

[130] Device Labeling Guidance #G91-1 (blue book memo)
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/default.htm

[131] Labeling. Regulatory Requirements for Medical Devices. CDRH PUBLICATIONS – MEDCAL DEVICES.

Ethicon Response: The inclusion of the requested statement is more problematic than might appear on initial scrutiny. On the basis of our discussion during the January teleconference, we believe that FDA's intent is to ensure that physicians have a better understanding of the information used to support market introductions for products of this type. However, there are numerous issues with the inclusion of the statement as appears above in our labeling:

1. We believe the statement could be actually be misleading, in that physicians may assume that products that do not include this statement in their IFU are supported by RCT studies demonstrating safety and effectiveness, which is not the case.

2. The statement could disadvantage us compared to competitors when working with payors for reimbursement of our device. Because this is a globally distributed product, the impact would reach far beyond the US borders to potentially create challenges in Europe, Australia, and other markets.
288

3. It is not clear to us that the statement is entirely accurate. A review of available literature identified several published studies that were randomized, controlled evaluations of transvaginal mesh intended to treat pelvic organ prolapse (Attachment III).

4. Inclusion of this statement would present a serious disadvantage to us from a marketing standpoint and would not result in a level playing field with respect to our competitors. Our current understanding is that the Boston Scientific Pinnacle device IFU, which has the same indication and was cleared in November 2007 (during the course of your review of our submission) without an RCT, does not contain this statement (K071957).

We believe that a least burdensome approach that should satisfy the intent of advising physicians about the basis for the device entering the market in the US would be to incorporate a statement such as the one below:
"In the US, the performance of GYNECARE PROLIFT Pelvic Floor Repair Systems as compared to synthetic mesh with the same indication has been demonstrated through benchtop and pre-clinical testing."

Or, alternately:
"In the US, substantial equivalence of GYNECARE PROLIFT Pelvic Floor Repair Systems to synthetic mesh with the same indication has been demonstrated through benchtop and pre-clinical testing."

> We believe that these statements indicate what information was used as the basis for device clearance, rather than speaking to what was not used. We have updated the IFU's for both devices (See Attachments I & II) to reflect the first approach above, but would be open to the alternate statement if FDA preferred.

(The FDA asked Ethicon to inform the user that there is no level-one evidence (the highest level of evidence) in support of the use of mesh in the treatment of POP. Ethicon offered four reasons why it shall not provide this information in the PROLIFT labels. Two of the four reasons related only to the fact that such disclosure might negatively impact sales. One of the remaining two reasons was based on a theoretical concern that users might somehow assume that the absence of this statement in the labels of other products indicates that level one evidence exists for such products. However, this statement, if true, would be equally correct for the converse. The absence of this statement from the PROLIFT IFU could suggest to the user that PROLIFT safety and efficacy is supported by level one evidence - similar to other products that do not make this statement. Additionally, the failure of one manufacturer to provide adequate disclosures is not justification for another to do the same. Finally, Ethicon suggests that the statement regarding the lack of level one evidence would not be accurate and cites six studies as evidence. Only four of these citations represent published studies (the remaining two appear only to be abstracts). Of these 4 published studies, only one involves permanently implanted mesh. This one study, by Hiltunen, et al., did not involve the use of guides (trocars), did not pull mesh arms through the obturator muscles or levator muscles, and combined mesh with native tissue surgery. Anyone versed in this field should be able to recognize that none of the six citations offered by Ethicon represent level one evidence demonstrating the safety and efficacy of synthetic mesh in the treatment of POP.)

Ethicon has deliberately chosen not to inform PROLIFT users of the lack of level one evidence supporting its device.

Expert Opinion on deviation from medical and or industry and or standards #11:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- The majority of surgeons rely on medical device companies as their primary or sole source of data with regard to safety and efficacy,
- Surgeons expect the safety and efficacy data provided by device companies to be complete, concise, and in no way misleading,
- Surgeons expect medical device companies to disclose uncertainties and missing evidence, and
- Medical device companies are aware that many surgeons rely on them as the primary and or sole source of safety and efficacy data and expect to be informed uncertainties and missing evidence.
- Ethicon has purposefully omitted from its label uncertainties and missing evidence and makes it clear that such has been omitted for the purpose of maximizing profitability.
- I can say to a reasonable degree of medical certainty that many surgeons would not have implanted PROLIFT if they had been informed of these facts.

Deficiencies and responses continued:

e. As stated in the predicate device labeling, your device should be contraindicated for implantation into pregnant women and implantation into areas with active and latent infection.

Ethicon Response: We have updated the IFU's, Attachments I & II, to reflect the above change. Please note that the proposed labeling had already contraindicated for implantation in pregnant women.

(Ethicon here admits that a contraindication was mission from its original label. This is evidence of misbranding. Misbranding is a violation of the law.)

Expert Opinion on deviation from medical and or industry and or standards #12:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect device companies to disclose all contraindications it its device labeling and industry standards dictate the inclusion of such contraindications.
- Ethicon's omission of this important contraindication contributed to the contamination of implants and resultant infection.

Deficiencies and responses continued:

g. Please add to your list of adverse events, the following: hematoma, urinary incontinence, urinary retention/obstruction, void dysfunction, pain, infection, adhesions, wound dehiscence, nerve damage, recurrent prolapse, contracture, and procedure failure.

Ethicon Response: We have updated the IFU's, Attachments I & II, to reflect the above changes. Please note that the proposed labeling had some of these adverse events already listed.

(Only 3 of these warnings (contraction, infection, and adhesion) had been previously included in the Ethicon labeling. Ethicon here admits that it had omitted warnings from its original label. This is evidence of misbranding. Misbranding is a violation of the law.)

Expert Opinion on deviation from medical and or industry and or standards #13:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect device companies to disclose all warnings in its labeling and industry standards dictate the inclusion of such warnings.
- Ethicon's omission of this important warnings caused significant patient morbidity including but not limited to wound dehiscence, nerve damage, urinary incontinence, urinary retention, and hematoma.

Deficiencies and responses continued:

g. Please add a warning to your labeling to recommend surgeons perform cystoscopy to confirm bladder integrity or to detect bladder perforation.

Ethicon Response: We have updated IFU's, Attachments I & II, to reflect the above change. Please note that on the basis of the discussion around this requested statement, we have also added the following warning to each IFU: "A digital rectal exam should be performed to detect possible rectal perforation."

(The warning "A digital rectal exam should be performed to detect possible rectal perforation" was omitted from the original label. This is evidence of misbranding. Misbranding is a violation of the law.)

Expert Opinion on deviation from medical and or industry and or standards #14:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect device companies to disclose all warnings in its labeling and industry standards dictate the inclusion of such warnings.
- Ethicon's omission of this important warnings caused significant harm to patients including but not limited to rectal perforation, rectal erosion of mesh, obstruction of the rectum with resultant severe constipation, chronic pain, and additional surgeries to mitigate complications.

Ethicon was aware of the suggestion to include a recommendation that "surgeons perform cystoscopy to confirm bladder integrity or to detect bladder perforation" in the warning section of its label. However, Ethicon knowingly opted not to use this warning and, instead, used the warning that "cystoscopy may be performed to confirm bladder and ureteral integrity". A manufacturer's warning that "recommends" cystoscopy compels such behavior. The word "may" in no way compels cystoscopy. As the majority of gynecologists are neither well trained in cystoscopy, nor have hospital privileges to perform cystoscopy, a warning that compelled cystoscopy would have been problematic to many users or potential users of the PROLIFT. The deliberate omission of such compelling language from the PROLIFT label allowed surgeons not well trained in cystoscopy and those without cystoscopy privileges to implant PROLIFT without performing a cystoscopy.

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Ethicon's deliberate omission of the recommendation to perform cystoscopy resulted in significant harm to patients, including but not limited to ureteral injury, bladder injury, fistula formation, and

additional surgeries to mitigate complications, and a corporate decision to omit such language must have, in large part, been predicated on a desire to increase sales volume.

h. Please add the following references to the last page of your labeling:

i. Huebner M, Hsu Y and Fenner DE. The use of graft materials in vaginal pelvic floor surgery. International Journal of Gynecology and Obstetrics 2006; 92:279-288.

ii. Altman D and Falconer C. Peri-operative morbidity using transvaginal mesh in pelvic organ prolapse repair. Obstetrics and Gynecology 2007; 109 (2, Part 1): 303-308.

Ethicon Response: As discussed in the conference call on 1/22/08, we believe it would be inappropriate to point to the specific studies when the body of literature available is constantly changing. We believe that relevant risk information from these studies has been captured in the warnings, precautions, and adverse events in our IFU's. We feel a least burdensome approach is to direct surgeons to obtain further information on transvaginal mesh literature through our sales representatives, who can provide lists of available literature that have been screened for fair balance through our internal copy review process. This approach has the additional benefits:

1. ETHICON can maintain a more current list of available literature through our sales representatives then we can manage through updates to the IFU.
2. It eliminates the need to translate the references into 28 languages (or more) since these products are globally distributed, each time the list would be updated.

Therefore, we suggest the following statement, which is prominently placed before the indications statement in both IFUs:

"Additional information on the clinical performance of mesh for pelvic floor repair is available in published literature. Contact your company sales representative for assistance."

Please refer to Attachment I & II for the updated IFUs.

(Ethicon, in this instance, states that its sales representatives should be providing surgeons with medical literature on transvaginal mesh and that such literature should first undergo an Ethicon internal screening and, following such screening, Ethicon will provide surgeons only with the literature it deems fair and balanced. This is an unusual confession. Ethicon discloses that it will

not be making peer reviewed literature on transvaginal mesh available to surgeons, but rather, will be making only a portion that it deems fair and balanced available. There is no evidence that Ethicon disclosed this policy to surgeons (in its label or elsewhere). Furthermore, Ethicon includes ongoing observational performance data in subsequent labeling without disclosing that Ethicon-paid consultants and employees are generating such data. Ethicon has admitted that it is presenting a biased snapshot of the transvaginal mesh literature to its users and this is evidenced in its labeling.)[132]

Expert Opinion on deviation from medical and or industry and or standards #15:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- The majority of surgeons rely on medical device companies as their primary or sole source of data with regard to safety and efficacy,
- Surgeons expect the safety and efficacy data provided by device companies to be complete, concise, and in no way misleading,
- Medical device companies are aware that many surgeons rely on them as the primary and or sole source of safety and efficacy data,
- Ethicon has created and implemented a policy of providing biased data to surgeons, and that such behavior by Ethicon deprives surgeons of valuable data that would mitigate against the implantation of the PROLIFT device.
- The result of such Ethicon behavior could only be an increased number of PROLIFT implants and PROLIFT related injuries.

Deficiencies and responses continued:

i. Please develop a Patient Brochure (patient labeling) to be provided when counseling the patient regarding options for treating pelvic organ prolapse. This brochure should address the following items. Please provide a draft patient labeling for review.

   i. Explanation of pelvic organ prolapse, including anatomical issues, causes and symptoms;
   ii. Treatment options (e.g. Pessaries, traditional surgical repair and surgical repair with mesh);

[132] ETH.MESH.02341660

iii. Risks and benefits of the various treatment options (including a reference to the FDA MAUDE database website at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE and instruction to reference product code = FTL);
iv. Statement to the effect that safety and effectiveness of mesh for vaginal repair have not been proven in randomized, controlled clinical studies; and
v. Statement to the effect that safety and effectiveness of mesh for vaginal repair have not been proven in randomized, controlled clinical studies; and
vi. Instructions for post-operative care.

Ethicon Response: Based on the discussion during our conference call on 1/22/08, we believe that our Patient Brochure addressed FDA's concerns above with the exception of including the updated risk information we've incorporated into the IFU on the basis of this review process. We have provided the patient brochure with updated language in the "What are the Risks?" Section (Attachment IV). A twin brochure for the GYNECARE PROLIFT + M System will also be provided to physicians for their use in educating patients about this disease state and possible use of our device – both brochures will have the same language in the risks section.

(Although the FDA provides Guidance for the Premarket Notification Applications for Surgical Mesh, this does not obviate the FDA guidelines for medical devices.[133] Such guidance states, "Risk/benefit information is information people need to decide to use a device or have it used on them," "This information also allows the users to become aware of potential problems with the device", "Inform and educate people about risks by using risk comparisons that compare risks that are similar or closely related," and "Avoid using vague or unfamiliar terms (e.g. "some women"). Such guidance also states that the manufacturer should "Test the medical device patient labeling with a sample of appropriate users of the device. This is the only way to know if the medical device patient labeling is understandable and useful." The FDA also indicates that the manufacturer "should acknowledge uncertainties, including lack of currently available scientific knowledge." The FDA has provided, via this deficiency, guidance to assist Ethicon in providing the necessary "information people need to decide to use a device or have it used on them" and, simultaneously, stay in compliance with the laws governing patient labeling.

Ethicon knowingly omitted from the PROLIFT product patient labeling the risks and benefits of treatment options. The provision of such treatment options would have allowed the patient to compare risks that may be similar

[133] Labeling. Requlatory Requirements for Medical Devices. CDRH PUBLICATIONS – MEDCAL DEVICES. Aug. 1989

or closely related and deprived patients of vital information necessary for making an informed decision on whether or not to have the device used on them. Even more concerning is the fact that Ethicon provided misleading and vague language with regard to alternative treatment options. Ethicon stated that a pessary "may help to relieve symptoms of mild prolapse." However, pessaries are equally helpful in treating the symptoms of moderate and severe prolapse. Ethicon stated that a patient may need to need to see the health care provider for "regular" check-ups. Regular is a vague term that could easily be misinterpreted to mean "frequent." The standard of care for pessary cleaning is quarterly (every 3 months). Ethicon knowingly omitted the fact that safety and efficacy and had not been demonstrated in randomized controlled clinical trials. In addition, the referenced Attachment IV, the patient brochure, includes misleading factual errors. The brochure states that there is a "small risk" of mesh material becoming exposed into the vaginal canal. Not only is the word "small" vague and prohibited by FDA labeling guidelines, Ethicon's TVM study had already demonstrated a greater than 10% incidence of mesh exposure. The brochure states that the procedure "can be completed in less than half the time of traditional surgery." Not only was evidence lacking to support this statement, it is the opposite of the truth; transvaginal mesh procedures require more time to perform than traditional surgery.[134] Perhaps of greatest concern is the misleading statement that PROLIFT "allows for the restoration of sexual function by restoring normal vaginal anatomy." As discussed elsewhere in this monograph in greater detail, the transvaginal implantation of PROLIFT is associated with a high incidence of moderate to severe vaginal contraction and vaginal banding.[135] This certainly is not a restoration of sexual function by restoration of normal vaginal anatomy. Indeed, the inventor of the PROLIFT procedure reported that PROLIFT was five times more likely to cause dyspareunia (compared to traditional native tissue surgery).[136] In addition, the brochure states that the PROLFIT procedure is performed "through very small incisions in the vagina." Not only are the words "very small" vague and prohibited by FDA labeling guidelines, the incisions utilized for PROLIFT implantation are neither very small, nor small. Most surgeons performing PROLIFT make an incision that is near or greater than 50% of the vaginal length, and this incision is described in the teachings of Ethicon.[137]

The use of vague and misleading language is a form of misbranding. A failure to disclose material fact is a form of misbranding. The failure to disclose uncertainties and lack of currently available scientific language is a form of

---

[134] Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD004014. DOI: 10.1002/14651858.CD004014.pub5

[135] ETH.MESH.00012009 and Eth.48281 (Scott Jones, product director reports "Regardless of how doctors adjust the mesh, there is still a definite ridge or banding that can be vaginally palpated with our anterior mesh")

[136] Fatton B, Lagrange E, Jacquetin B. Sexual Outcome After Transvaginal Repair Of Pelvic Organ Prolapse (Pop) With And Without Mesh: A Prospective Study Of 323 Patients. ICS Abstract.

[137] ETH.MESH.03960118 ("The recommended incision for the repair is a sagittal colpotomy starting 1 cm below the cervix and ending approximately 1 cm from the bladder neck".)

misbranding. The failure to disclose known risks and complications creates an inadequate label, which is a form of misbranding. Misbranding is a violation of the law.

The failure to disclose the risks and benefits of alternative treatment options, the use of misleading language with regard to alternative treatments (suggesting that the pessary treats only mild prolapse symptoms and that the use may necessitate "regular" returns to the physician for care), and the failure to disclose areas lacking scientific knowledge all prevented patients from making an informed decision of whether or not to undergo the implantation of PROLIFT and caused many patients to be implanted with resultant harm.)

Expert Opinion on deviation from medical and or industry and or standards #16:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect patient labels to be accurate, honest, factual, non-misleading, and routinely utilize patient labels such as brochures as part of the patient education consenting process;
- Manufacturers are typically aware that surgeons utilize patient labels as part of the patient education and consenting process;
- Standard industry practice dictates the use of accurate, honest, factual, and non-misleading language in patient labels;
- Ethicon knowingly created a patient label (brochure) that contained misleading language, factual errors, and failed to provide important information necessary for a patient to make an informed decision as to whether or not to be implanted with PROLIFT;
- The misleading and erroneous information in the PROLIFT device's brochure, as well as the deliberate exclusion of information from the label, resulted in a bias that would lead the patient toward choosing to be implanted with PROLIFT. This resulted in increased PROLIFT implantations and injuries.

Deficiency Three: Recommended changes to labeling for your PROLIFT + M device were outlined in our last letter requesting additional information. However, the revised labeling was not submitted as part of this supplement and one of the revisions requested was not accepted by you. Please address the following deficiencies.

Deficiency 3 a) There are no apparent clinical trials data on PROLIFT + M. Therefore, the device labeling should clearly distinguish Gynecare PROLIFT from Gynecare PROLIFT + M, stating that limited data from two prospective, non-randomized, non-controlled observational studies are available on a mesh material similar to PROLIFT used for vaginal prolapse repair, but that no clinical data exists for the combination absorbable/nonabsorbable material used in PROLIFT +M.

Ethicon Response: We have updated the GYNECARE PROLIFT + M IFU to include the following statement in the "Clinical Performance" section with the intent to distinguish between data available for GYNECARE PROLIFT and GYNECARE PROLIFT + M:

> "Randomized, controlled clinical evaluations of the GYNECARE PROLIFT and GYNECARE PROLIFT + M Systems are underway, but at this time preliminary data are available from two early observational studies of transvaginal mesh that were initiated in 2004. These observational studies evaluated a pre-cut surgical mesh made of the same non-absorbable polypropylene as the mesh used in the GYNECARE PROLIFT System but that did not incorporate the absorbable component found in the GYNECARE PROLIFT + M."

Please refer to Attachments I & II for the updated IFU's.

(Ethicon followed the instructions of the FDA and provided a PROLIFT +M IFU update that notified the user that the preliminary data comes from a study that used a mesh that did not incorporate the absorbable component found in PROLIFT +M. However, Ethicon also knowingly omitted the clinical performance data from that that study, performance data that included a failure to reach a pre-determined success metric, data that was included in its PROLIFT IFU. These data are meaningful and relevant to those considering the use of PROLIFT +M. The two devices have the same Indication for Use, use the same surgical instruments and methods, and differ only in composition of the mesh. Following the absorption of the poliglecaprone component of the PROLIFT +M mesh, the remaining mesh is lighter than and has a lower burst strength than the PROLIFT mesh. Hence, the fact that the heavier and stronger PROLIFT device (mesh) failed to meet its clinical performance success criterion is quite relevant to a potential user of the PROLIFT +M device (mesh). The omission of material facts is a form of misbranding. Misbranding is a violation of the law.)

Expert Opinion on deviation from medical and or industry and or standards #17:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons consider performance data on similar devices as important when making a decision to use or not use a device with limited data,
- Ethicon knowingly omitted the PROLIFT performance data from the PROLIFT +M label (IFU), and the omission of the PROLIFT performance data from the PROLIFT +M IFU favored an increased number of PROLIFT +M implants with resultant injury.

Deficiency 3 b) We do not agree that inclusion of a statement regarding the strength loss of the PROLIFT + M mesh as the poliglecaprone component is absorbed would be meaningless or potentially confusing to the surgeon. Please include the statement "As the absorbable component of the mesh degrades, the percent loss of burst strength from pre-absorption (135 psi) to post-absorption (90 psi) is approximately 33%" in your device description section in your device labeling.

Ethicon Response: While the company agrees that mesh strength is an important device characteristic for the surgeon to understand, we continue to disagree with the position that information on the burst strength for the device should be presented in terms of what is lost following the absorption of the absorbable component of the mesh. The device was designed to meet a specific user need regarding strength, and that user need is met by the mesh post-absorption. The statement above is misleading in that it implies that the product itself suffers some degradation after absorption occurs. As previously described, there is ample burst strength in the naked mesh itself to withstand any forces observed in the pelvic floor. Inclusion of such a misleading statement creates the opportunity for our competitors to disparage our device when, in fact, the device performs as intended with regard to burst strength, since the incidental burst strength conveyed by the absorbable component is not a required part of the device design. To try to address the concern that physicians understand the level strength of the mesh post-absorption, the following statement is proposed:

> "After absorption of the poliglecaprone-25 component, only the polypropylene mesh remains, which has a burst strength of approximately 90 pounds per square inch (psi)."

We hope that you will work with us to reach an acceptable compromise regarding this information. Please refer to Attachment II for the updated GYNECARE PROLIFT + M IFU.

(As noted elsewhere in this monograph, Ethicon has not evaluated the post-absorption burst strength in vivo (the burst strength after implantation, following absorption of the poliglecaprone, and again following degradation of the polypropylene component). Ethicon only bench tested the burst strength of its mechanically cut, naked ULTRAPRO (ULTRAPRO without the poliglecaprone).[138] This bench testing of naked ULTRAPRO tells us little about the in vivo strength following degradation of the polypropylene component. Ethicon also knowingly excludes any comparative reference to the burst strength of its GYNEMESH PS, the mesh used in its observational study that failed to meet its success criteria. The burst strength of the naked ULTRAPRO was found to be approximately 23% less than that of GYNEMESH PS.[139] These data relevant to those considering the implantation of PROLIFT +M. Failure to disclose material facts is a form of misbranding. Misbranding is a violation of the law.)

Expert Opinion on deviation from medical and or industry and or standards #18:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons consider performance data on similar devices important when making a decision to use or not use a device with limited data,
- Ethicon knowingly omitted the burst strength of its GYNEMESH PS (a metric that would have given significant meaning to the reported 90 PSI reported for the PROLIFT +M), and the omission of GYNEMESH PS data favored an increased number of PROLIFT +M implants with resultant injury.

Deficiency 3 c): Please confirm the removal of the statement "the bi-directional elastic property allows adaptation to various stresses encountered in the body" in your revised labeling.

Ethicon Response: The "bi-directional" statement has been removed from both the GYNECARE PROLIFT and GYNECARE PROLIFT + M IFUs. Please refer to Attachments I & II for the updated IFUs.

[138] ETH.01065

[139] ETH.01301

(Ethicon has agreed to remove the misleading statement, "the bi-directional elastic property allows adaptation to various stresses encountered in the body." However, this misleading claim existed in the PROLIFT label of the un-cleared but marketed PROLIFT device for the previous two years. Also, it does not appear that existing labeling was changed for several years. The first IFU I have discovered with this modification is labeled 02/2010.[140] Misleading statements represent misbranding. Misbranding is a violation of the law.)

Expert Opinion on deviation from medical and or industry and or standards #19:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons consider bidirectional elasticity a desirable property for any graft material used to treat pelvic organ prolapse,
- The claim for bidirectional elasticity was never demonstrated post-implantation, and
- The claim of bidirectional elasticity was misleading and caused surgeons to choose PROLIFT as their implant device with resultant patient injury.

Deficiency Four: As outlined in our last request for additional information, you have not provided data to support the following statement regarding elastic properties of the PROLIFT and PROLIFT + M systems. Please remove the statement "the bi-directional elastic property allows adaptation to various stresses encountered in the body" from your labeling for the PROLIFT Pelvic Floor System. Please submit revised instructions for use for review.

Ethicon Response: The "bi-directional" statement has been removed from both the GYNECARE PROLIFT and GYNECARE PROLIFT + M IFUs. Please refer to Attachments I & II for the updated IFUs.

(Expert Opinion: Same as noted for deficiency 3 c).

Deficiency Five: The mechanical testing data and summary that you have provided for your PROLIFT and PROLIFT + M meshes are incomplete. The PROLIFT Mesh is different in shape than the PROLENE Mesh. In your device labeling, you also state that "the mesh [PROLIFT] is constructed of reduced

[140] ETH.MESH.02341658 (copyright 2009)

diameter multifilament fibers, knotted into a unique design that results in a mesh that is approximately 50% more flexible than standard PROLENE mesh." Please provide data for arm pull-out, burst strength, suture pull-out, tear strength, tensile strength, and flexural rigidity testing of the PROLIFT Mesh. Please also provide data for the PROLIFT + M Mesh arm pull-out test. The data provided should include at minimum the average values, standard deviations, and sample sizes for all requested tests.

Ethicon Response: We have provided a complete updated Feature Comparison Table and Attachment V with data including average values, standard deviations, and sample sizes for the requested tests. In some cases, the table has been updated from the previously submitted table to reflect more recent data.

PROLIFT + M:
The manufacture of GYNECARE PROLIFT + M mesh differs slightly from its base material, ULTRAPRO mesh. PROLIFT + M mesh is laser-cut as opposed to mechanically cut ULTRAPRO mesh. Therefore, the applicable mechanical testing has been re-performed using laser-cut PROLIFT + M mesh as the base material (e.g. tensile strength, flexural rigidity, suture pull-out strength, Mullen burst strength, and tear strength). These test results demonstrate that PROLIFT + M mesh has properties that are substantially equivalent to predicate devices.
In addition, PROLIFT + M mesh has been tested for arm tensile strength as well as arm pull-off strength. Arm tensile strength is the tensile strength of the arm alone. Test results for arm tensile strength are substantially equivalent to the predicate devices, APOGEE and PERIGEE. These results are also comparable to pre-cut versions of the GYNEMESH PS and ULTRAPRO mesh predicate devices.
Arm pull-off testing is conducted to ensure that the mesh implants can withstand the forces applied during a procedure. Prior testing determined the force required pull a PROLIFT + M mesh implant arm through the cannula to be 0.73 lbf. Based on this data and the data collected during performance testing, it can be concluded that the PROLIFT + M mesh implant has adequate strength to withstand the forces applied during insertion (13.5 lbf).

PROLIFT:
The manufacture of GYNECARE PROLIFT mesh differs slightly from its base material, PROLENE Soft Mesh (or GYNEMESH PS). PROLIFT mesh is laser-cut as opposed to ultrasonically cut GYNEMESH PS mesh. Therefore, the applicable mechanical testing has been re-performed using laser-cut PROLIFT mesh as the base material (e.g. tensile strength, flexural rigidity, suture pull-out strength, Mullen burst strength, and tear strength). These test results demonstrate that PROLIFT mesh has properties that are substantially equivalent to the predicate devices. In addition, PROLIFT mesh has been tested for arm tensile strength as well as arm pull-off strength. Arm tensile strength is the tensile strength of the arm alone. Test results for arm tensile strength are substantially equivalent to the predicate devices, APOGEE and PERIGEE. These results are also comparable to pre-cut versions of the GYNEMESH PS and ULTRAPRO mesh predicate devices.

Arm pull-off testing is conducted to ensure that the mesh implants can withstand the forces applied during a procedure. Prior testing determined the force required to pull a PROLIFT + M mesh implant arm through the cannula to be 0.73 lbf. Based on this data and the data collected during performance testing, it can be concluded that the PROLIFT mesh implant has adequate strength to withstand the forces applied during insertion (12.0 lbf).

(Although the bench testing of the arms performed by Ethicon may have satisfied the FDA data request, no testing was done on the naked arms of PROLIFT + M. Ethicon recognized that the PROLIFT + M mesh post-absorption would have substantially different composition and material properties, compared to the implanted PROLIFT + M, and had reported previously to the FDA on the burst strength of the "naked" ULTRAPRO (the PROLIFT +M mesh with the poliglecaprone removed). However, in performing the bench testing of the PROLIFT + M arms, it does not appear as though testing was performed on "naked" arms. The referenced "Attachment V" shows "pre-absorption" and "post-absorption" testing on the ULTRAPRO and PROLIFT + M, but this description is conspicuously missing from the rows and columns for the PROLIFT + M arms. Hence, the data recorded and reported on PROLIFT + M arms is not meaningful. The arm pull-off testing (PROLIFT + M and PROLIFT) was neither performed through the cannula, nor in vivo. Hence, the data is not meaningful with regard to the intended method of use. At the time of this response, Ethicon had received six reports of PROLIFT arms pulling off during surgery.)[141]

Expert Opinion on deviation from medical and or industry and or standards #20:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Ethicon was aware that it had not evaluated the post-absorption properties of the PROLIFT +M arms,
- Ethicon was aware that the stronger and heavier PROLIFT arms had been periodically pulling off during implantation,
- Ethicon did not inform surgeons of the risk of PROLIFT arm avulsion and tearing,
- Ethicon did not inform surgeons of a potentially increased risk of PROLIFT +M arm failure,
- Ethicon did not teach mitigation for arm failure,

[141] ETH.08120, ETH.08141, ETH.08246, ETH.08253, ETH.09149, ETH.09275

- Surgeons expect device companies to disclose the risks of device failure and teach mitigation for the same, and
- "Naked" pull-off data, had it been collected, could have decreased surgeon usage of the PROLIFT +M device.

Deficiency Six: You have provided a revised 510(k) summary and new predicate devices, K040537 and K040623. However, these new predicate devices are not listed in your 510(k) summary. Please include these predicate devices and submit a revised 510(k) summary.

Ethicon Response: We have updated the 510(k) summary to include the referenced predicate devices. Please refer to Attachment VI for the updated 510(k) summary.

Deficiency Seven: You have provided reports of clinical studies to support your device performance in response to our last letter request for additional information. However, a financial disclosure statement could not be found in your supplemental submission. Please submit a financial disclosure statement as required by 21 CFR §54.

Ethicon Response: It is ETHICON's opinion that the TVM studies are not covered studies as defined in 21 CFR §54, as they were post-market evaluations not intended to support any regulatory submissions. However, as per our discussion on 1/22/08, we have made a concerted effort to obtain financial disclosures from the investigators who participated in the two studies (France and US) back in 2004. Investigators were contacted by mail to obtain the requested information.

At this point in time, financial disclosures are available from only 3 of the 11 investigators, despite efforts to obtain this information. Participants in the French study provided two responses and a US participant provided one. The US investigator reported earnings from the sponsor in excess of $25,000 at the time of study initiation due to payments for consultation, honoraria, proctoring, and preceptoring. In addition, this individual left his medical practice and ended his role as an investigator upon accepting employment with the sponsor.

Although the information is incomplete, the sponsor does not believe financial interests introduced bias into the studies. The following steps were undertaken to reduce study bias: a) Investigational sites were monitored by trained personnel who had access to study and subject medical records. The review of medical records address the quality of the data collection and confirmed reporting of all adverse events. The reviews verified compliance with the protocol. b) A key secondary endpoint, the PSI/QOL values are completed by the subjects themselves.

Please reference Attachment VI for financial disclosure information.

(Ethicon provides, as rational for its failure to disclose its financial relationship with its TVM investigators, that the TVM studies were post-market evaluations that were not intended to support any regulatory submissions (therefore exempt from 21 CFR §54). However, this is a nonsensical stance. This letter is part of Ethicon's regulatory submission, its 510 (k), for the PROLIFT devices and the TVM data are being submitted in support of this submission. The intention of the study is not relevant. Section 54.3 requires Ethicon to submit its certified disclosures. Section 54.1(b) notifies applicants that the FDA will be reviewing the financial disclosures for potential causes of study bias (financial interest of investigators) such as "royalty" agreements or other proprietary interest in the product.

Sec 54.3 states, "The requirements in this part apply to any applicant who submits a marketing application for a human drug, biological product, or device and who submits covered clinical studies. The applicant is responsible for making the appropriate certification or disclosure statement where the applicant either contracted with one or more clinical investigators to conduct the studies or submitted studies conducted by others not under contract to the applicant. Section 54.2(a) notifies the applicant of particular concern for "Compensation affected by the outcome of clinical studies means compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest." Ethicon provides financial disclosure from only three of the eleven investigators. Yet, Ethicon opted not to disclose other financial relationships it was aware of, including paid consultant agreements with U.S. investigators and a royalty agreement with Dr. Jacquetin, a form of significant study bias specifically called into question by 21 CFR §54.[142] The undisclosed financial relationships, if disclosed, could have significantly delayed the FDA clearance of the PROLIFT products.

> Sec. 54.5, Agency Evaluation of Financial Interests, states "(c) Agency actions to ensure reliability of data. If FDA determines that the financial interests of any clinical investigator raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data including:
>
> (1) Initiating agency audits of the data derived from the clinical investigator in question;
>
> (2) Requesting that the applicant submit further analyses of data, e.g., to evaluate the effect of the clinical investigator's data on overall study outcome;

[142] The consulting and royalty agreement for Dr. Jacquetin is discussed and cited elsewhere in this monograph.

(3) Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and

(4) Refusing to treat the covered clinical study as providing data that can be the basis for an agency action."

Although Ethicon describes the steps it took to control bias, none of these measures can control for financial bias of investigators who are subjectively evaluating success and reporting complications.)[143]

Expert Opinion on deviation from medical and or industry and or standards #21:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Ethicon knowingly omitted financial disclosures that would have demonstrated significant study bias,
- Surgeons expect to be informed of such financial bias and consider such when evaluating studies,
- Financial bias reporting is a standard in the medical literature, device manufacturers are aware of the fact that surgeons expect to be informed of financial bias in device studies,
- Ethicon knowingly omitted such financial disclosures from its labels that included the referenced biased data, and the omission of the material facts related to the financial bias in the TVM studies resulted in increased implantation of PROLIFT devices with associated patient injury.

In **May of 2008,** the FDA notified Ethicon of two additional deficiencies.[144] The FDA stated: "The labeling changes that have been and are being requested are labeling changes that are being requested during review of premarket notifications for mesh indicated for use in treatment of pelvic organ prolapse. This is part of an ongoing process to provide more accurate and informative labeling to both physicians and patients in response to an increase in receipt of adverse event reports related to the

[143] Antosh DD, Iglesia CB, Vora S, Sokol AI. Outcome assessment with blinded versus unblinded POP-Q exams. Am J Obstet Gynecol 2011;205:489.e1-4. These investigators demonstated that the POP-Q examination, used to measure success or failure in the TVM study, is prone to bias with non-blinded examiners underestimating recurrence 15% of the time.

[144] ETH.01311

use of large, specially shaped mesh with the use of surgical tools to facilitate placement in a "blinded" procedure for the treatment of pelvic organ prolapse. Please address the following two deficiencies:

Deficiency One: Previously, we requested that you include the following statement in your device labeling: "The safety and effectiveness of synthetic mesh or film support in transvaginal surgical procedures to treat pelvic organ prolapse have not been demonstrated in prospective, randomized clinical trials."
This request was made due to the lack of evidence of the safety and effectiveness for transvaginal/transobturator/etc. placement of large, specially shaped mesh with the use of surgical tools to facilitate placement in a "blinded" procedure for the treatment of pelvic organ prolapse through study in controlled, prospective, randomized clinical trials. We have considered your response to this request, however, we stand firm in our request to include the above requested language in your labeling. We propose the following statement, which includes your suggested wording, to be included in your labeling:

> "The safety and effectiveness of this mesh compared to conventional surgical repair for pelvic organ prolapse have not been demonstrated in randomized controlled clinical trials. In the United States, substantial equivalence of Gynecare PROLIFT Pelvic Floor Repair Systems to synthetic mesh with the same indication has been demonstrated through benchtop and cadaveric testing."
> Please include the statement in your device labeling for both the PROLIFT and PROLIFT + M mesh systems**.**

Ethicon Response: Ethicon agreed to comply.[145]

Deficiency Two. Previously, we requested that you provide patient labeling. Prior to submission of this supplement, you presented a sample of your patient labeling for cursory review and we had discussed with you, via teleconference, our recommendations on labeling revisions. You have provided labeling with proposed changes for review in this supplement. Please address the following deficiencies that remain with your revised patient labeling.

a. Please include the following statement in your patient labeling: "Synthetic mesh is a permanent medical device implant. There are not enough data from clinical studies to know whether the benefits of this implant are greater than the risks. Therefore, you should carefully discuss with your doctor and understand the pros and cons of mesh implants before deciding on a procedure to treat your condition."

Ethicon Response: We must disagree with FDA regarding the statement that the data (pre-clinical and clinical) available are insufficient to determine whether the benefits of the device are greater than the risks. The basis for our CE-marking of the device is a

[145] ETH.01318 (May 9th 2008)

Clinical Expert Report that evaluates existing clinical information (including the market experience from approximately 100,000 devices sold), pre-clinical information, and a rigorous risk analysis process to conclude that the benefits of the device outweigh the risks. We therefore respectfully request that the statement be included as amended below:

> "Synthetic mesh is a permanent medical device implant. Therefore, you should carefully discuss with your doctor and understand the benefits and risks of mesh implant surgery before deciding how to treat your condition."

Please refer to Attachment 3 for the text for the revised pages of the patient brochure. Pages of the patient brochure that did not require modification can be seen in Attachment 4.

(At the time of writing this response, Ethicon was already in possession of its biased one-year French TVM data that failed to meet its pre-determined success (benefit) criteria, yet demonstrated a 14% incidence of mesh extrusion and a 12.6% incidence of moderate to severe vaginal contraction. These short-term data, collected by investigators that included the financially incentivized, non-blinded inventor of the PROLIFT procedure, certainly called into question the risk/benefit ratio. At the time of the writing of this response, investigators of the Ethicon TVM study had already submitted for publication data on 684 patients undergoing the TVM procedure that demonstrated a 33.6% complication rate (77 granulomas or prosthetic expositions (11.3% [6.7% in the vaginal anterior wall, 2.1% in the vaginal posterior wall and 4.8% in the fornix]), 80 prosthetic retractions (11.7%), 36 relapse of prolapse (6.9%) and 37 SUI de novo (5.4%) with a mean follow-up of only 3.6 months.[146] Regardless of Ethicon's findings in the Clinical Expert Report it prepared for its CE mark application, the findings of its prospective French TVM study and the data being published by its investigators would certainly now raise the question of whether the risks outweighed the benefits. Indeed, a meaningful risk/benefit analysis cannot be rendered without a prospective randomized trial (or, at a minimum, an observational study with a native tissue cohort). Ethicon here knowingly omits from its patient label the fact that that there is no ability to determine relative risk without a cohort or control group (preferentially a native tissue cohort or control). Failure to disclose uncertainties and missing evidence is a form of misbranding. Misbranding is a violation of the law.)

Expert Opinion on deviation from medical and or industry and or standards #22:

> As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of

[146] Caquant, Fréderic, Pierre Collinet, Philippe Debodinance, Juan Berrocal, Olivier Garbin, Claude Rosenthal, Henri Clave, Richard Villet, Bernard Jacquetin, and Michel Cosson. "Safety of Trans Vaginal Mesh Procedure: Retrospective Study of 684 Patients." .Journal of Obstetrics and Gynaecology Research 34.4 (2008): 449-56.

testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect patient labels to be accurate, honest, factual, non-misleading, and to disclose uncertainties and missing evidence,
- Surgeons routinely utilize patient labels, such as brochures, as part of the patient education consenting process;
- Manufacturers are typically aware that surgeons utilize patient labels as part of the patient education and consenting process;
- Standard industry labeling practice dictates the use of accurate, honest, factual, non-misleading language that discloses uncertainties and missing evidence;
- Ethicon here knowingly excluded uncertainties and missing evidence for its patient label (brochure);
- This deliberate omission would make a patient more likely to choose to be implanted with PROLIFT. This resulted in increased PROLIFT implantations and injuries.

Deficiencies and responses continued:

b. Please provide supporting data from clinical studies for the following statement (p. 13, last paragraph, first sentence) or remove it from your patient labeling: "Pelvic floor repair procedures with Gynecare PROLIFT are appropriate for most patients, even those who have undergone previous operations for pelvic organ prolapse or stress incontinence."

Ethicon Response: We have revised the statement as appears below to remove the implied claim that would require clinical data support. This generic statement simply encourages the patient to consult her physician and also conveys several of the contraindications for the device.

> "You may be a candidate for treatment with the GYNECARE PROLIFT system if you have been diagnosed with pelvic organ prolapse. As with any surgery of this kind, this procedure should not be performed on pregnant women, infants or children. It should also not be considered by women who plan a future pregnancy. Only a complete physical examination and consultation with your physician can determine which procedure is right for you."

Please refer to Attachment 3 for the text for the revised pages of the patient brochure. Pages of the patient brochure that did not require modification can be seen in Attachment 4.

(Ethicon here admits that it has no clinical data to support the claim that PROLIFT is appropriate for most patients. Yet, this claim appears on a PROLIFT patient brochure with a 2005 copyright date.[147] Furthermore, Ethicon has declared previously that PROLIFT is not appropriate for most patients, but rather, “For those cases where an

[147] ETH.02000

adequate surgical repair is not possible without additional supporting or bridging material."[148] Ethicon's claim of the appropriateness of PROLIFT for most patients is a contradiction to its previous claim and misleads patients. Misleading is a form of misbranding. Misbranding is a violation of the law.)

Expert Opinion on deviation from medical and or industry and or standards #23:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect patient labels to be accurate, honest, factual, non-misleading, and to disclose uncertainties and missing evidence,
- Surgeons routinely utilize patient labels such as brochures as part of the patient education consenting process;
- Manufacturers are typically aware that surgeons utilize patient labels as part of the patient education and consenting process;
- Standard industry labeling practice dictates the use of accurate, honest, factual, non-misleading language that discloses uncertainties and missing evidence;
- Ethicon here knowingly creates a misleading patient brochure that creates the impression that all women are candidates for PROLIFT implantation. This would make a patient more likely to choose to be implanted with PROLIFT. This resulted in increased PROLIFT implantations and injuries.

Deficiencies and responses continued:

c. Please remove p. 3 of your patient labeling. The text presented on this page is promotional, biased, and can be perceived as coercive to the patient to use your device. In addition, the basic content of this page is presented elsewhere in your patient labeling, therefore, its removal would not alter the informative value of this labeling to patients.

Ethicon Response: We agree to remove Page 3 of the patient brochure (as shown in Attachment 2). We propose, however, to incorporate the information on disease prevalence into the "What Is Pelvic Organ Prolapse" section that is found on the current Page 4 of the patient brochure. This information is highlighted below and would be incorporated as follows:

What is pelvic organ prolapse?

[148] ETH.00928

> Would it surprise you to learn that while it's rarely talked about, half of all women over age 50 experience some degree of pelvic organ prolapse? By age 80, more than one out of every 10 women will have undergone surgery for prolapse. Pelvic organ prolapse can affect a woman's daily life, limiting physical and sexual functioning. Normally the vagina and uterus are secured to the pelvis by connective tissue that forms ligament-like structures as well as a strong "envelope" around the vaginal walls. As pelvic floor muscles weaken, these connective structures give way, allowing the vagina to become displaced towards, and at times beyond the vaginal opening. The bladder above and the rectum below the vagina are thereby affected, leading to the following symptoms...

Please note that the following sources were used to provide the statistics regarding the prevalence of the disease: American Journal of Obstetrics and Gynecology; V.180; No.2; Pt.1; 2/99; p299, Olsen AL, Smith VJ, Bergstrom JO, et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997; 89:501-6.
This article is available at http://www.medforum.nl/gynfo/leading_article10.htm

(Ethicon here agreed to remove language from the patient brochure that an expert in labeling has described as promotional and biased and coercive to the patient to use PROLIFT. This language appeared in the PROLIFT patient brochure with a copyright date of 2005.[149] Hence, this biased and coercive language had most likely been in public circulation for three years. The language contemplated there includes the statement “You can do something about pelvic organ prolapse and you have choices in the GYNECARE PROLIFT pelvic floor repair system, a revolutionary surgical technique that offers promising results for women with pelvic organ prolapse.” In addition to being biased and coercive, the word “revolutionary” is ambiguous and misleading. The use of ambiguous or misleading language, especially language that tends to create a false impression, is a form of misbranding. Misbranding is a violation of the law.)

Expert Opinion on deviation from medical and or industry and or standards #24:

> As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:
> - Surgeons expect patient labels to be accurate, honest, factual, non-misleading, and to disclose uncertainties and missing evidence,

[149] ETH.02000

- Surgeons routinely utilize patient labels, such as brochures, as part of the patient education consenting process;
- Manufacturers are typically aware that surgeons utilize patient labels as part of the patient education and consenting process;
- Standard industry labeling practice dictates the use of accurate, honest, factual, non-misleading language that discloses uncertainties and missing evidence;
- Ethicon herein knowingly created a misleading patient brochure that created the impression that the PROLIFT device represents a revolutionary device. The definition of revolutionary includes "being or bringing about a big or important change".[150] This would make a patient more likely to choose to be implanted with PROLIFT. This resulted in increased PROLIFT implantations and injuries.

Deficiencies and responses continued:

d. Please remove the word "special" from the phrase "special synthetic material" (p. 9, 1st paragraph, last sentence) as it is inappropriate to refer to a synthetic material as special.

Ethicon Response: We agree to remove the word "special" from the phrase "special synthetic material" in the patient brochure. Please refer to Attachment 3 for the text for the revised pages of the patient brochure. Pages of the patient brochure that did not require modification can be seen in Attachment 4.

(Ethicon here agreed to remove ambiguous language from its patient brochure. This language appeared in the PROLIFT patient brochure with a copyright of 2005.[151] Hence, this ambiguous language, typical of trade puffery, had most likely been in public circulation for three years. Ambiguous language and trade puffery constitutes misbranding. Misbranding is a violation of the law.)

Expert Opinion on deviation from medical and or industry and or standards #25:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect patient labels to be accurate, honest, factual, non-misleading, and to disclose uncertainties and missing evidence,

[150] http://www.merriam-webster.com/dictionary/revolutionary

[151] ETH.02000

- Surgeons routinely utilize patient labels such as brochures as part of the patient education consenting process;
- Manufacturers are typically aware that surgeons utilize patient labels as part of the patient education and consenting process;
- Standard industry labeling practice dictates the use of accurate, honest, factual, non-misleading language that discloses uncertainties and missing evidence;
- Ethicon herein knowingly created a misleading patient brochure that created the impression that the PROLIFT device utilized a better or "special" mesh. This would make a patient more likely to choose to be implanted with PROLIFT. This resulted in increased PROLIFT implantations and injuries.

Deficiencies and responses continued:

e. Please replace the phrase "a sling procedure performed at the same time" with "other interventions" within the sentence "... some women may have stress urinary incontinence and may require a sling procedure performed at same time to correct urinary incontinence" as sling procedure is not the only option available for treatment of stress urinary incontinence.
Ethicon Response: We agree to replace the phrase "a sling procedure" as requested above. The revised wording will appear as follows:

"For example, some women may have stress urinary incontinence and may require additional treatment to correct it."

We felt that the term "interventions" might be confusing to a layperson, so we slightly modified the phrase to address that. Please refer to Attachment 3 for the text for the revised pages of the patient brochure. Pages of the patient brochure that did not require modification can be seen in Attachment 4.

(Ethicon herein acknowledges that language in a patient brochure may be confusing to a layperson. However, it provides not evidence that it has tested this language or other language in its labels. Label testing is an industry standard. Ethicon is aware of the process of label testing. By way of example, Ethicon tested its GYNEMESH PS IFU label.)[152]

Expert Opinion on deviation from medical and or industry and or standards #26:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge,

[152] FINAL REPORT, PSE ACCESSION NO. 02-0317 Design Validation (Human Factor) for GYNECARE GYNEMESH PS

training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Ethicon was aware of the standards for label testing,
- Ethicon picked and choose ambiguous language to the benefit of sales, rather than to the benefit of the patient, and this behavior resulted in increased PROLIFT implantations with associated patient injury.

Deficiencies and responses continued:

f. Please include statement under the "What are the risks?" section (p. 13) which reflects that one of the most common adverse event[s] is mesh extrusion and this complication usually requires the removal of the mesh and may interfere with sexual function.

Ethicon Response: We have revised the "What are the risks?" section on page 13 as follows to address FDA's concern above:

"All surgical procedures present risks. Complications associated with the procedure include injury to blood vessels or nerves of the pelvis, difficulty urinating, pain, scarring, bladder and bowel injury. There is also a risk of the mesh material becoming exposed into the vaginal canal. Mesh exposure can be associated with pain during intercourse for the patient and her partner. Exposure may require treatment such as vaginal medication or removal of the exposed mesh."

This information is based on our Medical expert's input on the standard means of treating mesh exposures, many of which resolve spontaneously or with medication. In cases where additional surgery is needed, typically only the exposed mesh material is removed, not the entire implanted device. We have elected to retain the use of the word "exposure" rather than "extrusion" since exposure is both an accurate description of what may occur but also is a lay-term appropriate for use in patient-directed labeling. Extrusion would imply that the implant itself could somehow be forced out an opening in tissue, and this is not what occurs, clinically.

(The PROLIFT patient brochure with a copyright of 2005, published approximately 3 years prior to this proposed update, stated "there is also a small risk of mesh becoming exposed in the vagina."[153] This was the only warning regarding mesh exposure. Yet, in 2005, the Principle Investigator and a sub-investigator of the Ethicon-sponsored TVM study had already published an observed 12% incidence of mesh exposure at only 2 months following implantation.[154] Furthermore, these same

[153] ETH.02000

[154] Collinet, Pierre, Franck Belot, Philippe Debodinance, Edouard Ha Duc, Jean-Philippe Lucot, and Michel Cosson. "Transvaginal Mesh Technique for Pelvic Organ Prolapse Repair: Mesh Exposure Management and Risk Factors." .International Urogynecology Journal Int Urogynecol J</i> 17.4 (2005): 315-20.

investigators reported that only 1/3rd of these mesh extrusions responded to conservative management and the others underwent surgical intervention. They acknowledged that their findings were consistent with those of other investigators. These TVM investigators concluded, "Nowadays, based on these data, we can only advise that caution be exercised when carrying out this new surgical procedure. In fact, experimental studies and clinical trials seem necessary in order to reduce the level of exposure to less than 5% of cases." These findings were validated by a subsequent report by these and other investigators of the French TVM study (including the inventor of the PROLIFT method and shapes, Dr. Jacquetin).[155] These investigators found an approximately 11% incidence of mesh exposure at a mean period of only 3.6 months following implantation. They evaluated over 600 patients undergoing the TVM surgery. Similar to the previous publication, these investigators found that the majority of exposures did not respond to medical management and required surgical intervention. The final French TVM report, dated June of 2006, documented a 10% rate of mesh exposure.[156]

Hence, during the approximate 3 years between the publication of the PROLIFT patient brochure in 2005 and the proposal of this new brochure language, Ethicon instructed patients that there was a "small risk of mesh becoming exposed in the vagina," even though it was well aware of at least a 10% risk of this complication. Not only is a description of "small risk" ambiguous, it is unlikely that a patient would consider a 10% risk of a complication that was likely to require additional surgery a "small risk." Furthermore, Ethicon's internal policy for evaluating device safety considers complications that are unlikely to be those that occur less than one in a million times.[157] A 1 in 10 risk of erosion would not be considered unlikely. Indeed, this same Ethicon policy describes events that occur with a 1 in 10 frequency to be "almost inevitable" and 1 in 20 to be "situation repeatedly occurs." Ethicon failed to disclose the material facts and used ambiguous, misleading language. This is a form of misbranding. Misbranding is a violation of the law. In 2008, Ethicon is in receipt of additional information putting it on further notice that mesh exposure is a common complication (not rare) and usually requires intervention. Rather than update its patient label to include the known incidence and known consequences of this potentially disabling complication, Ethicon knowing omits such information from its update. Ethicon's label update removes the words "small risk" and substitutes "there is a risk" and adds that "exposure may require treatment." However, Ethicon knew from its prospective observational study and the published data of its investigators

---

155 Caquant, Fréderic, Pierre Collinet, Philippe Debodinance, Juan Berrocal, Olivier Garbin, Claude Rosenthal, Henri Clave, Richard Villet, Bernard Jacquetin, and Michel Cosson. "Safety of Trans Vaginal Mesh Procedure: Retrospective Study of 684 Patients." .Journal of Obstetrics and Gynaecology Research</i> 34.4 (2008): 449-56.

156 ETH.MESH.00012009

157 ETH.MESH.03742864-03742891 2007 Attachment I - OP650 -011v6 Rating & Risk Categorization Tables, used for the 2005 PROLIFT market introduction.

that the incidence of exposure was most likely greater than 10% (later studies would find rates over 20%) and that mesh exposure typically requires treatment. Ethicon once again knowingly omits material facts and misleads the patient. This is once again misbranding and a violation of the law.)

Expert Opinion on deviation from medical and or industry and or standards #27:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect patient labels to be accurate, honest, factual, non-misleading, and to disclose uncertainties and missing evidence,
- Surgeons routinely utilize patient labels such as brochures as part of the patient education consenting process;
- Manufacturers are typically aware that surgeons utilize patient labels as part of the patient education and consenting process;
- Standard industry labeling practice dictates the use of accurate, honest, factual, non-misleading language that discloses uncertainties and missing evidence;
- Ethicon herein knowingly published a misleading patient brochure that created the impression that downplayed the incidence of a known and difficult to treat complication of the PROLIFT and, when reminded of such, knowingly continued to publish similarly misleading information. This would make a patient more likely to choose to be implanted with PROLIFT. This resulted in increased PROLIFT implantations and injuries.

On **May 15th of 2008,** Ethicon received official notice from the FDA of determination of substantial equivalence giving Ethicon clearance to legally market its PROLIFT and PROLIFT +M devices (in the U.S.).[158]

Summary Expert Opinion on deviation from medical and or industry and or standards:

Although Ethicon may have convinced the FDA that its PROLIFT device had not been illegally marketed for over two years and its new PROLIFT+M was substantially equivalent to legally marketed devices, as described above, neither the PROLIFT, nor the PROLIFT +M were substantially equivalent. Hence, safety and efficacy had not been established through the regulatory pathway. It

[158] ETH-01894

is, however, important to remember that the FDA is not the party responsible for establishing safety and efficacy.

The manufacturer is responsible for ensuring safety and efficacy. Ethicon had every opportunity to perform the necessary laboratory testing, animal testing, and voluntary prospective human clinical trials to demonstrate safety and efficacy. Ethicon's initial sidestepping of the FDA regulations set in place to provide a minimum level safety and efficacy for the patient and Ethicon's later successful deception of the FDA that lead to an incorrect SE determination with resultant bypassing of the rigorous testing required in a PMA in no way prohibited Ethicon from or released Ethicon of its ethical and corporate obligation to perform, on its own accord, the testing necessary to demonstrate safety and efficacy. During the 2005 to 2008 timeframe of the illegal marketing of the PROLIFT device, Ethicon knowingly withheld material facts and misled both physicians and patients, creating false impressions and encouraging use of a dangerous device. Following its receipt of additional expert advice with regard to the increasing number of complications, lower than expected efficacy, and need for improved labeling, Ethicon once again opted to omit material facts, uncertainties, and critical warnings from its patient and physician labels. Ethicon discloses that, at least in part, its decisions to withhold such information from its labeling was predicated on a concern for potentially negatively impacting sales.

In **January of 2012,** the FDA issued Ethicon a 522 Order for its PROLIFT device. The FDA informed Ethicon that its PROLIFT device was reasonably likely to cause "serious adverse health consequences" and "was intended to be implanted in the body for more than one year." Either of these circumstances can cause an order for postmarket surveillance. The FDA informed Ethicon that it was "concerned with the potential safety risks as evidenced by adverse events reported to the FDA and in the published literature" and, in addition, was "concerned with the published literature indicating a lack of added clinical benefit compared to non-mesh repair."

This order required Ethicon to submit its plan for postmarket surveillance that addressed a series of questions provide by the FDA. The FDA informed Ethicon that it would review their plan and responses and "determine whether the plan will result in the collection of useful data that can reveal unforeseen adverse events or other information necessary to protect the public health." The FDA recommended "a randomized clinical trial (RCT) or prospective cohort study design that compares your device(s) to a control (e.g., transvaginal urogynecologic surgery without use of mesh) through 3 years of follow-up."

On **February 1st of 2012,** Ethicon submitted its plan to the FDA.[159] This plan did not contain any RCT data collection for PROLIFT and offered an ongoing PROLIFT + M RCT by Dr. Withagen. On **April 2nd of 2012,** Ethicon was notified by the FDA of

[159] ETH.MESH.07724600

numerous deficiencies in its plan. On **May 9th of 2012,** Ethicon notified the FDA that, in light of the complexities of the clinical study requirements, adverse publicity, and the litigation environment, it would be discontinuing the commercialization of its PROLIFT device.[160]

On January 4th of 2016, the FDA reported that it had reclassified transvaginal prolapse mesh from a moderate-risk device to a high-risk device. Coincident to this, it issued the requisite order "that requires all manufacturers to submit a premarket approval application (PMA) to support the safety and effectiveness of surgical mesh for the transvaginal repair of POP. The orders will require manufacturers to address safety concerns, including severe pelvic pain and organ perforation, through a rigorous PMA pathway to demonstrate safety and effectiveness."[161] As noted elsewhere in this monograph, it was evident that PROLIFT was not substantially equivalent to a legally marketed device, had never demonstrated safety and efficacy, and should have gone through the PMA process prior to its marketing in 2005. As also noted elsewhere herein, nothing prohibited Ethicon from either submitting a PMA or performing typically related testing. Now, in the wake of 11 years of PROLIFT-related harm and unconsented experimentation on women throughout the U.S. and world, the FDA has declared PROLIFT (and other vaginal meshes) a high-risk device with a mandatory PMA.

THE CLINICAL DATA and ASSOCIATED COMMUNICATIONS

At the time of introduction of PROLIFT to the U.S. market in 2005, there were no published, peer reviewed data on the PROLIFT device or method and there were only two published papers on the PROLIFT prototype surgery, TVM. At the time of introduction of PROLIFT to the U.S. market there were a small amount of data available on the use of sheet mesh (no arms) in the treatment of pelvic organ prolapse. As no clinical trials had been performed with PROLIFT, Ethicon's Medical Director, Charlotte Owens, opted to rely on the scant body of evidence available for the transvaginal implantation of sheet mesh in the creation of her Clinical Expert Report. She did not include any of the retrospective data from the TVM group. Dr. Owens's report was necessitated as part of Ethicon's Design Requirement Matrix and, also, for regulatory submissions.[162] Dr. Owens offered only 1 study, a study of 24 women treated with a very different device that she believed supported the use marketing of PROLIFT. In addition, she offered two "communications."[163]

---

160 ETH.MESH.04005092

161 http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm479732.htm

162 ETH.MESH.00308845

163 ETH.07152

The Study: The one study offered by Dr. Owens in support of PROLIFT involved 24 women with two or more post-surgical recurrences of POP. Twelve women underwent a combination of native tissue surgery with reinforcement of the anterior compartment with Marlex (C.R. Bard) polypropylene mesh. This mesh was sheet mesh (no arms) that was sutured in place. Twelve women underwent native tissue repair without mesh. The authors found a significantly lower incidence of anterior anatomic failure in the Marlex group. However, the authors neither report any symptomatic benefit associated with the mesh implantation, nor report on recurrent prolapse of the non-treated compartments (compartments without mesh). As previously discussed, transvaginal mesh implantation is associated with an increased risk of de novo untreated compartment failure. More concerning, however, is the fact that 25% of women in the Marlex mesh group described symptomatic mesh exposure and only one of the three responded to procedural intervention. **In summary, this study of 12 women with a history of multiple POP recurrences randomized to MARLEX transvaginal mesh implantation (a mesh without arms and of different construction than GYNEMESH PS) did not show any symptomatic benefit (versus Native tissue repair), but did demonstrate a 25% incidence of symptomatic and non responsive mesh erosion (66% did not respond to treatment).**

Communication: Dr. Owens also offered an unpublished study by Foote, et al., which ostensibly involved a 6 month follow-up of 29 women undergoing posterior repair with PROLENE. Dr. Owens reported that the study demonstrated a 93% cure rate at 6 months. Dr. Owens does not, however, disclose the 24% mesh extrusion rate.[164] There is no mention of a control group**. In Summary, this is an uncontrolled study of 29 women who underwent transvaginal implantation with PROLENE (a different mesh than the GYNEMESH PS of PROLIFT), experience a 24% incidence of mesh extrusion, and had 93% improvement with only 6 months follow-up.** I have searched Int. J. Urogynaecol, July 1997 and was not able to find the proposed publication.

Communication: Dr. Owens also offered a communication from Cervigini stating that this surgeon "reported the safe use of PROLENE mesh in the repair of anterior prolapse in 35 patients." This is an example of one of lowest levels of evidence. This is an anecdotal report of an uncontrolled case series of a no-arm mesh that is different than the GYNEMESH PS of PROLIFT. **In summary, this is an anecdotal report that states that a surgeon has used a sheet mesh, without arms and different than GYNEMESH PS, safely to treat anterior prolapse. Although not disclosed by Dr. Owens, Cervigini subsequently published an abstract of a randomized controlled trial of women treated with Pelvicol (xenograft from**

[164] ETH.MESH.01154036 (Gynemesh PS Expert Report by Dr. Weisberg)

C.R. Bard) and GYNEMESH PS (PROLENE Soft).[165] Cervigini, et al., found no significant anatomic benefit associated with GYNEMESH. The authors also found an 8 fold greater incidence of GYNEMESH PS extrusion.

2004 (Berrocal, et al.):

The PROLIFT procedure (method and shapes) was invented by French surgeon, Dr. Jacquetin. Dr. Jacquetin and his French colleagues began performing the PROLFIT prototype surgery, TVM, somewhere between 2000 and 2002. After performing approximately 300 prototype surgeries, in **November of 2004**, they published their description of the TVM procedure. This publication by the "TVM Group" described what would be later called the PROLIFT procedure and also presented the TVM group's assessment of the use of transvaginal mesh in the treatment of POP.[166] This group was under the logistical and material management of Gynecare.[167]

The authors declared that "Placement of a mesh not only aims at reducing the recurrence rate, but has other objectives such as obtaining a tension-free repair, radically minimizing postoperative pain, reducing difficulty in the passing of feces, and preventing stenosis and dyspareunia."[168] However, at the time of this publication, they were unable to offer their 300 cases as evidence that such objectives were obtained. Indeed, today, twelve years later, the overwhelming pool of evidence suggests that these objectives were never obtained. The authors cite a "conventional procedure" recurrence rate of 20-30% and, years later, their one-year prospective TVM data would fall into this same range. Later reports by some of these same investigators demonstrated a 5 fold higher rate of dyspareunia associated with the TVM procedure.

These same authors (also TVM investigators), in this 2004 publication, stated "Our review of the relevant literature has been relatively disappointing." In addition to citing the same Julian paper referenced by Dr. Owens in her Clinical Expert Report, they cited Migliari, et al., stating that these investigators found a cure rate of 41% in patients treated for cystoceles with tension-free PROLENE mesh (at mean of 20 months). The authors of this TVM paper noted that the use of the anterior midline incision for the TVM procedure (the same incision taught in the PROLIFT labels) was associated with a 17.5% erosion rate and that this rate dropped to 2.7% if no such incision was made (implant performed through hysterectomy incision). The authors concluded that "this technique (TVM) should be reserved for the

---

165 Cervigni M, Natale F, Weir J, Galante L, Panei M, Agostini M, Pajoncini C, La Penna C1, Mako A, Spadaro S, . S.Carlo-IDI Hospital. PROSPECTIVE RANDOMIZED TRIAL OF TWO NEW MATERIALS FOR THE CORRECTION OF ANTERIOR COMPARTMENT PROLAPSE: PELVICOL AND PROLENE SOFT. ICS.org. Patients treated 2002-2004

166 ETH.02800

167 Berrocal J et al. Conceptual advances in the surgical management of genital prolapse: The TVM technique emergence. J. Gynecol Obstet Biol Reprod 2004; 33: 577.

168 Berrocal J et al. Conceptual advances in the surgical management of genital prolapse: The TVM technique emergence. J. Gynecol Obstet Biol Reprod 2004; 33: 578.

management of grade 3 and grade 4 prolapse" and indicated that a prospective trial had begun.

The concerning findings reported by the TVM group, the inventors of the PROLIFT procedure, discovered while under the management of Ethicon (Gynecare), were clearly known in 2004, yet conspicuously absent from both the Clinical Expert Report of Dr. Owens and the labels of PROLIFT marketed in 2005 and after.

2005:

(Milani, et al.):

In **January of 2005**, prior to the market release of PROLFIT, Milani, et al., **Functional and anatomical outcome of anterior and posterior vaginal prolapse repair with PROLENE mesh,**[169] was published. This prospective observational study of randomized 63 women to anterior or posterior repair colporrhaphies reinforced with tailored PROLENE mesh (Ethicon). The mesh was tailored to the patient's anatomy with the use of a sterile ruler. Although this combined technique demonstrated a 94% POP-Q success rate at 12 months, 12.5% of the anterior group and 63% of the posterior group suffered de novo dyspareunia. The authors noted that their previous posterior compartment study, utilizing the same technique without mesh, was associated with only 1/3rd the de novo dyspareunia rate.[170] The authors also documented a 13% anterior and 6.5% posterior mesh exposure (extrusion).

The authors concluded, "In summary this study confirms that, despite good anatomical results, the use of PROLENE mesh for prolapse repair carries morbidity especially in terms of erosion through the vaginal wall and de novo dyspareunia. On the basis of these data, we believe that the use of PROLENE mesh for prolapse repair should be abandoned. We believe that it is of outmost importance that the new prosthetic materials for prolapse surgery should be assessed not only for efficacy or erosion rate but also for bladder, bowel and sexual function."

(Collinet, et al.):

In **March of 2005,** the same month PROLIFT was introduced to the U.S. market, the investigators of the yet to be published prospective Ethicon French TVM study, submitted for publication their retrospective evaluation of 277 women who had

---

[169] Milani et al. Functional and anatomical outcome of anterior and posterior vaginal prolapse repair with prolene mesh. BJOG: an International Journal of Obstetrics and Gynaecology. January 2005, Vol. 112, pp. 107–111

[170] Milani R, Soligo M, Salvatore S, et al. Fascial defect repair for symptomatic rectocele: anatomical and functional outcome. Proceed- ings 33rd Annual Meeting of the International Continence Society — Florence, 5–9 October 2003, 2003:189–190. 20% incidence of de novo dyspareunia in posterior compartment repair that involved suturing the illeococcygeus muscle.

undergone the prototype PROLIFT surgery.[171] Within only 2 months of surgery, the authors had documented a 12% incidence of mesh exposure (extrusion), of which 74% required surgical excision. The authors of the 2004 paper on the prototype PROLIFT surgery noted a decrease in the mesh extrusion rate when they concomitantly stopped making the midline incision and substituted PROLENE Soft for PROLENE mesh. Those investigators were unable to determine if the decrease in extrusion rate was secondary to the abandonment of the vaginal incision and or the change to GYNEMESH PS. However, in this much larger study, the investigators found that the use of GYNEMESH PS was not associated with a lower extrusion rate. The authors concluded, as suggested by the 2004 publication, that "the number of colpotomies needed to be limited (to decrease mesh extrusion)." The authors stated, "These problems arise due to exposure of the mesh material caused by inadequate healing." Yet, in direct opposition to the findings of the only group of surgeons experienced with the prototype PROLIFT device and procedure, Ethicon included the following statement in its original and updated labels: "The mesh remains soft and pliable, and normal wound healing is not noticeably impaired."[172] Finally, the TVM investigators concluded, "Nowadays, based on these data, we can only advise that caution be exercised when carrying out this new surgical procedure. In fact, experimental studies and clinical trials seem necessary in order to reduce the level of exposure to less than 5% of cases."

These concerning, published findings and recommendations of Ethicon's TVM investigators, known at the time of initial and marketing of PROLIFT, were conspicuously absent from both the Clinical Expert Report of Dr. Owens (Ethicon's Medical Director) and PROLIFT labels and updates. Equally concerning is the fact that Ethicon ignored the recommendation of its experts and never performed the recommended experimental studies and clinical trials.

(Miller, et al.):

In **August of 2005,** Ethicon-paid consultant and key opinion leader, Dennis Miller, presented early finding of the U.S. and French TVM studies. The abstract, entitled "Trans-Vaginal Mesh (Tvm): An Innovative Approach To Placing Synthetic Mesh Transvaginally For Surgical Correction Of Pelvic Support Defects – Peri-Operative Safety Results," reported on the complications of 180 women (90 U.S. and 90 French) undergoing the prototype PROLIFT procedure.[173] Severe complications including hemorrhage, rectal injury, recto-vaginal fistula formation, vesicovaginal fistula formation, ureteral stricture and ureteral injury, and the less severe complications of urinary retention and hematoma were presented. The overall

---

171 Collinet, Pierre, Franck Belot, Philippe Debodinance, Edouard Ha Duc, Jean-Philippe Lucot, and Michel Cosson. "Transvaginal Mesh Technique for Pelvic Organ Prolapse Repair: Mesh Exposure Management and Risk Factors." .International Urogynecology Journal Int Urogynecol J</i> 17.4 (2005): 315-20.

172 ETH.MESH.02341658 (2010), ETH.MESH.02341522(2004)

173 ETH.MESH.00482987, ETH.MESH.02347163

complication rate was 9.5%. The severe complication rate was 5%.[174] It should be noted that Dr. Miller opted not to include complications such as vaginal contraction and de novo dyspareunia (and apareunia) or the well-documented complication of mesh extrusion. Yet, a high and concerning incidence of these complications would be reported only weeks later by the principle investigator of the French TVM study, Dr. Cosson.

(Cosson, et al.):

Published and presented in **September of 2005,** was the International Continence Society Abstract, PROLIFT (Mesh (Gynecare) For Pelvic Organ Prolapse Surgical Treatment Using The TVM Group Technique: A Retrospective Study Of 684 Patients.[175] This paper by Dr. Michel Cosson, the principle investigator of the French TVM study, and his coinvestigators (including the inventor of the PROLIFT procedure, Dr. Jacquetin) pointed out that PROLIFT was now available and "To date, little data is available on its effectiveness and possible complications. The aim of this study was to state its efficiency, but also intra- operative, short and medium terms post-operative complications." This retrospective study reported efficacy and complications at a mean of only 3.6 months. The investigators found a mean incidence of mesh extrusion to be 6.7%, with one center reporting 13.3%. The investigators also found a 5.3% failure rate. The principle investigator of the TVM study and his colleagues, the only surgeons with significant PROLIFT experience, interpreted their results. They were most concerned by the high rate of recurrent pelvic organ prolapse noted at only 3.6 months, "More worrying are high rates of OPR, all the more so as follow-up is rather short (mean of 3.6 months)." They also reported that the incidence of mesh extrusion "remained high regarding the impairment (it would) cause."[176]

The concerning findings of the principle investigator and co-investigators of Ethicon's prospective French TVM study were presented and published only 6 months after the introduction of U.S. marketing for PROLIFT. Although the investigators pointed out that there were little pre-existing data, they present troublesome data on both efficacy and complications associated with the "now available" PROLIFT device. Ethicon neither updated its labels with warnings, cautions, or new material facts, nor ceased marketing to initiate the previously recommended and now further substantiated need for experimental studies and clinical trials. The initiation of clinical trials would not only have provided critical information regarding safety and efficacy, it would have allowed women to be better informed prior to voluntarily undergo this dangerous surgery.

---

[174] When corrected for hysterectomy, severe complication rate is 4%.

[175] ETH-02351: Cosson M et al. Prolift mesh (Gynecare) for pelvic organ prolapse surgical treatment using the TVM group technique: a retrospective study of 687 patients. ICS Abstract 121, 9-2-2005.

[176] ETH-02351: Cosson M et al. Prolift mesh (Gynecare) for pelvic organ prolapse surgical treatment using the TVM group technique: a retrospective study of 687 patients. ICS Abstract 121, 9-2-2005. The authors use GF and VE to describe granulation and exposure and group them together.

Of great curiosity is the fact that the findings of these papers were not published (beyond the original abstract) until 2008. When published in 2008, the data were more concerning. Although the mean follow-up was still reported to be 3.6 months, the incidence of mesh extrusion was now reported to be significantly higher, at 11.3%. Also, the rate of recurrent prolapse was reported to be higher, 6.9%, and 11.7% of women were noted to exhibit vaginal retraction (contraction). Clearly, if the investigators were concerned about efficacy at the time of abstract, the concern would have been greater if they had these updated calculations. Of additional note, these authors once again observed an impressive variability of both efficacy and complications. This phenomenon, later validated by prospective data, should have raised great concern about the reproducibility of the procedure amongst general gynecologists in the community.

(Cosson, 1-Year Ethicon French TVM Report):

On **June 27th of 2006,** approximately 1.25 years since the introduction of PROLIFT to the U.S. market, over two years since the suggestions of the TVM group to limit the surgery to patients with stage 3 and 4 prolapse, and over one year since the recommendation of the TVM investigators that clinical trials be performed, the one year findings of the French TVM study were reported. Although the report was presented internally, it was not published in a publically available medical journal (and investigators were prohibited from publishing the data prior to the completion of the study, 5 years, and then, Ethicon reserved the right to approve such publication).[177] This was a prospective, non-randomized, observational study reporting on 87 women who underwent the prototype PROLIFT surgery.

Key Findings of the French TVM Study (reported at one year):

- **Failure exceeded the predetermined criterion of 20% (Upper CI) at both 6 months and one year.[178]**
  - **One year failure rate (POP-Q G2) was 18.4% with upper CI at 26.6%.**
- **Success varied from 50% to 100% between sites (8 sites)**
- **Moderate to severe contraction 12.6%**
- **Mesh Exposure 10% (majority were taken to surgical intervention). 5/9 (55% underwent at least one surgical intervention for mesh exposure).**
- **75% of patients experienced at least one adverse event**
- **45 women (50% of enrolled patients) required treatment for an adverse event.**

[177] ETH.MESH.00401366,57,59,63,65,66

[178] ETH.MESH.00401354 The choice of 20% as the maximum rate of recurrence was developed following a literature review and discussions with experts in the field of pelvic floor repair (urologists and urogynecologists).

- **10% of women suffered from a severe adverse event.[179]**
- **Approximately 18% of patients went to a related re-operation.[180]**
- **De novo dyspareunia 8.0%.[181]**
- **Substantial decrease in sexually active women following the TVM procedure (Decrease from 61-40).**

The authors of this Ethicon-sponsored study included the (financially motiovated) inventor of the PROLIFT procedure and his peers. These authors concluded, "The results of the study do not fulfill the criteria of success." However, they subsequently offered that "the recurrence rates compared favorably with re-operation rates of around 30% using traditional vaginal surgeries." This biased (inventor and financial bias) statement is nonsensical and statistically incorrect. In order to compare the results of the procedures, TVM versus native tissue surgery, the authors must compare recurrence rates to recurrence rates or, more appropriately, perform the clinical trial they recommended in 2005. Of the 16 patients re-operated on during the 12 month TVM study period, only 2 were operated on for recurrent POP. This means that 14 patients with recurrent POP may still undergo re-operation. The authors herein suggest that the re-operation rate following traditional vaginal surgery is "around 30%" and cite a single prospective trial. This 1996 prospective trial by Benson, et al., randomized 42 patients to vaginal surgery.[182]Although Benson reported a 33% re-operation rate at 2.5 years, all but 4% were represented by recurrent cystoceles. Hence, the study showed a 29% re-operation rate for recurrent anterior compartment failure (and only 4% for other compartments). The 29% incidence of re-operation rate is, however, not truly representative of re-operation following native tissue surgery. Benson, et al., excluded all patients exhibiting a cystocele secondary to isolated midline defects (those patients most likely to respond to native tissue surgery). Hence, the one prospective study cited by the incentivized TVM authors does not demonstrate an "around 30%" re-operation rate for traditional vaginal surgeries, but rather demonstrates a 29% re-operation rate for a unique and high risk group of patients and a 4% re-operation rate for other patients. The French TVM authors also bizarrely concluded, "This study demonstrates low mesh exposure and complication rates and an acceptable safety profile." The mesh extrusion rate reported at one year was 10%; two of the investigators previously that "experimental studies and clinical trials seem necessary in order to reduce the level of exposure to less than 5% of cases."[183] Multiple TVM investigators, including the PROLIFT method inventor, Bernard Jacquetin, declared only 9

---

179 ETH.MESH.00012061

180 This number is corrected for un-related re-operations such as cholecystecomy, femur fracture, and examination under anesthesia). ETH.MESH.00012064-68

181 3 new cases of dyspareunia reported amongst 40 sexually active patients.

182 Vaginal versus Abdominal Reconstructive Surgery for the Treatment of Pelvic Support Defects: A Prospective Randomized Study with Long-term Outcome Evaluation." International Journal of Gynecology & Obstetrics 57.1 (1997): 113. Web.

183 Collinet, Pierre, Franck Belot, Philippe Debodinance, Edouard Ha Duc, Jean-Philippe Lucot, and Michel Cosson. "Transvaginal Mesh Technique for Pelvic Organ Prolapse Repair: Mesh Exposure Management and Risk Factors." .International Urogynecology Journal Int Urogynecol J</i> 17.4 (2005): 315-20.

months earlier, in reference to their retrospective study of 684 TVM patients, that the 6.7% rate of mesh extrusion "remained high regarding the impairment (it would) cause."[184]

In summary, the Ethicon-sponsored French TVM study of 87 women, performed by incentivized investigators, failed to meet its success criterion. The demonstrated mesh extrusion rates previously described as high and needing reduction by its investigators, associated with an 18% incidence of re-operation for serious adverse events, resulted in a 12.6% incidence of moderate to severe vaginal contraction, and was associated with an 8% incidence of new dyspareunia (over 4 x greater than native tissue according to subsequent report from Dr. Jacquetin). These one-year data provided no evidence of superiority to native tissue surgery, yet demonstrated high and novel morbidity. In addition, it demonstrated that there was a great variability of efficacy amongst highly trained pelvic surgeons. In complete disregard for the growing pool of non-reassuring and concerning data, Ethicon neither initiated randomized controlled trials (in which patients could be informed and voluntarily undergo the experimental PROLIFT procedure), nor ceased to market the PROLIFT device. Ethicon also opted not to publish the findings of this study. Ethicon would eventually add several data points to its IFU label where, as discussed elsewhere, the failures of the studies to demonstrate success or safety were never clearly communicated.

(Robinson, 1-Year Ethicon U.S. TVM Report):

On **June 28th of 2006,** the day after the reporting of the French TVM data, the U.S. TVM data was reported. Although the report was presented internally, it was not published in a publically available medical journal (and investigators were prohibited from publishing the data prior to the completion of the study, 5 years, and then, Ethicon reserved the right to approve such publication).[185] This was a prospective, non-randomized, observational study reporting on 85 women who underwent prototype PROLIFT surgery.

Key Differences from the French TVM Study:

- **The French study utilized the Total PROLIFT method, whereas the U.S. study allowed anterior, and/or posterior, or Total PROLIFT.**
- **The French study was to include only patients with grade 3 or greater POP, whereas the U.S. study allowed the inclusion of the less severe grade 2 POP.**
- **The French study reported on the concerning complication of vaginal retraction (contraction), whereas the U.S. study did not.**

---

184 ETH-02351: Cosson M et al. Prolift mesh (Gynecare) for pelvic organ prolapse surgical treatment using the TVM group technique: a retrospective study of 687 patients. ICS Abstract 121, 9-2-2005. The authors use GF and VE to describe granulation and exposure and group them together.

185 ETH.MESH.00401366,57,59,63,65,66

The U.S. study reported on decreased vaginal compliance, but did not define what this was or how it was measured.

- **Previous or concurrent hysterectomy was required in the French study.**

Key Findings of the U.S. TVM Study (reported at one year):

- **Failure exceeded the original protocol's predetermined criterion of 20%.[186]**
  - **One year failure rate was 12%-14%.**
- **66% of patients experienced at least one adverse event.**
- **Mesh Exposure rate at 14%.**

The one-year findings of the U.S. TVM study, like the French study, showed a high rate of mesh extrusion, a rate that was substantially higher than the upper limit of 5% proposed by the French inventors and investigators of the PROLIFT procedure. Although the (incentivized biased) authors of this report conclude that the study provides evidence of a prolapse recurrence rate of less than 20%, the authors do not disclose that the recurrence rate, as defined by the original protocol and subsequent "Confidential Statistical Analysis Plan" met the study pre-determined failure criteria."[187] The authors draw the same incorrect conclusion and cite the same single prospective study comparing the TVM surgery to traditional vaginal surgery. The TVM study did not compare favorably to the once-referenced prospective study on traditional vaginal surgery. Although the authors describe a decrease in dyspareunia, there is neither a qualitative assessment, nor a delineation of de novo dyspareunia, a complication of TVM described by the French TVM investigators. The 51% baseline incidence rate of dyspareunia reported by the U.S. investigators is remarkably higher than both that reported in the general population and the 7% reported by the French TVM investigators. This creates even more concern for the methods used in defining dyspareunia and draws into further question the one-year dyspareunia incidence of 2.3% reported by the U.S. investigators. Furthermore, this 2.3 % is approximately 5 times less than the rate of post-PROLIFT dyspareunia reported by the inventor of the procedure.[188] Also curious is the only one case of reported untreated compartment failure (1% rate of untreated compartment failure). Subsequent prospective studies of PROLIFT demonstrated up to a 53% rate of untreated compartment failure.[189]

---

[186] ETH.MESH.00401365 Ethicon's TVM protocol provided that a recurrence rate of 0.13 would be considered a failure.

[187] ETH.MESH.00401470-71. Ethicon's CONFIDENTIAL STATISTICAL ANALYSIS PLAN stipulated that all missing data would be considered a recurrence at that such data would be utilized for confirmatory analysis. Additionally, several patients seem to have been counted as failures at 6 months but not at one year. The inclusion of these patients as failures would further increase the failure rate ETH-75916-75917; ETH-75591-75592. Dr. David Robinson, one of the 3 investigators of the U.S. TVM study serves employed by Ethicon as its World Wide Medical Director from November of 2005 to December of 2010. (https://www.linkedin.com/in/davidrobinson21). Dr. Lucente was a paid consultant of Ethicon since January 21st of 2005 and would get paid to lecture and train surgeons on PROLIFT. ETH.MESH.00366804.

[188] Fatton B, Lagrange E, Jacquetin B. Sexual Outcome After Transvaginal Repair Of Pelvic Organ Prolapse (Pop) With And Without Mesh: A Prospective Study Of 323 Patients. Department of Gynecology. ICS Abstract. University Hospital of Clermont-Ferrand. France, Department of Gynecology. University Hospital of Clermont-Ferrand. France.

[189] Milani AL, Withagen MIJ, Vierhout ME. Outcomes and predictors of failure of trocar-guided vaginal mesh surgery for pelvic organ prolapse.. Am J Obstet Gynecol 2012;206:440.e1-8. Withagen, M, et al. Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse. Amer Coll Obstet and Gyn 2011; 117:No2,Pt1.

In summary, the Ethicon-sponsored U.S. TVM study of 85 women, performed by incentivized investigators, failed to meet its success criterion and demonstrated mesh extrusion rates previously described as high and needing reduction by the inventors and pioneers of the procedure. The dyspareunia data were remarkably different than those demonstrated by the French Investigators, surgeons with many more years of experience with TVM. Although this should have caused Ethicon to explore the data for accuracy and, if accurate, determine and instruct surgeons what the U.S. investigators did to achieve this decreased dyspareunia rate, this never occurred. Based on the conflicting findings of the French TVM group and the prospective data that followed, the accuracy of the U.S. data remain suspect. Additionally, the 1% incidence of untreated compartment failure was 20-50 times less than that reported by subsequent prospective studies and creates even further concern for the accuracy of the U.S. TVM data.

Expert Opinion on Ethicon's 1-Year Prospective French and U.S. Data and its Response to Such:

Neither the one-year French, nor the U.S. prospective observational data on the prototype PROLIFT procedure provided evidence of superiority to native tissue surgery, yet both studies demonstrated high and novel morbidity. Both studies failed to meet the pre-defined success criteria. Both studies raised substantial concerns of high re-operation rates. This constellation of lack of efficacy and high complication rates combined with conflicted findings (U.S. vs. French Studies) and dramatic differences in efficacy between centers necessitated randomized clinical trials. These trials were needed to further explore the concerns of safety and efficacy raised by the pre-existing pool of retrospective data and these new and non-reassuring prospective data. If expert pelvic surgeons who developed the method were unable to demonstrate safety and efficacy, this would be less likely in the hands of the less skilled general gynecologic and urologic surgeons. Ethicon neither ceased to market PROLIFT, nor initiated a randomized controlled trial. This caused surgeons to continue to implant PROLIFT in women without demonstrated safety and efficacy. Although the purpose of the Ethicon-sponsored French and U.S. TVM studies was to demonstrate safety and efficacy, Ethicon never published, nor otherwise made available to surgeons these one-year findings. Furthermore, the protocol prohibited the investigators from disclosing the results of the study until the 5-year study was complete.[190] It is also very important to note that the overwhelming majority of the procedures were performed without the PROLIFT tools or laser cut shapes and, therefore, any findings of limited efficacy and or safety could not be extended to the PROLIFT device, a device already being marketed. Ethicon never repeated the study with the PROLIFT device that was actually marketed.

[190] ETH.MESH.00401355,57,59,63,65,66

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony, and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- The majority of surgeons were unaware of the paucity of data supporting the use of PROLIFT the growing pool of concerning data on PROLIFT,
- Had surgeons been aware of the lack of supportive data and the growing pool of concerning data, it would have discouraged their use of PROLIFT,
- Ethicon and the inventors of the PROLIFT procedure and device were aware of the paucity of data supporting the use of PROLIFT,
- Ethicon and the inventors of PROLIFT were aware of the growing pool of concerning data on PROLIFT,
- Ethicon ignored the advice of its inventors to perform a clinical trial,
- Both the limited retrospective data on prototype PROLIFT surgery and the new one year French and U.S. TVM data failed to demonstrate an improvement in efficacy (vs. traditional surgery),
- Both the limited retrospective data on prototype PROLIFT surgery and the new one year French and U.S. TVM data demonstrated a very concerning rate of complications and novel complications,
- Ethicon knowingly withheld the one-year prospective data from surgeons and obstructed the dissemination of such data, creating a deviation from industry and ethical standards, and
- Ethicon's failure to perform clinical trails to demonstrate safety and efficacy both prior to marketing and in the face of a growing pool of concerning data post-marketing represents a deviation from industry standards.

(Fatton, et al.):

Between **September 6th and 9th of 2006**, Dr. Fatton and four other investigators from the Ethicon's French TVM study presented their retrospective TVM data at the 31st Annual IUGA Meeting in Athens, Greece. This presentation was in the form of a poster abstract titled Preliminary Results Of The PROLIFT Technique In The Treatment Of Pelvic Organ Prolapse By Vaginal Approach: A Multicentric Retrospective Series Of 110 Patients.[191] These patients all featured POP at, or beyond, the hymenal ring. The authors neither disclose the mean follow, nor the fact that their anatomic success and complications are at only 3 months post PROLIFT implant.[192] The authors report that shrinkage of the mesh was noted in 17% of patients and failure was noted in 4.7% of patients. Based on these data points, the authors conclude that PROLIFT is a safe

[191] Fatton B et al. Preliminary results of the "Prolift" technique in the treatment of pelvic organ prolapse by vaginal approach: A multicentric retrospective series of 110 patients [abstract]. Int Urogynecol J 2006; 17 (Suppl 2): S212-213.

[192] Fatton B, Amblard J, Debodinance P, Cosson M, Jacquetin B. Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (ProliftTM technique) - a case series multicentric study. Int Urogynecol J 2007; 18: 743-752.

technique to correct pelvic organ prolapse. The authors did, however, add to their conclusion, "Anatomical results must be assessed with along term follow-up to confirm the effectiveness of the procedure. We have to assess more precisely functional and sexual outcomes before to extend the indications of PROLIFT to young women or for primary prolapse repair." It is unlikely that any surgeon or person versed in the field would consider 3-month retrospective data evidence of safety or efficacy. Although the authors reported that their work was not industry supported, at least one author was under a royalty agreement with Ethicon (would be paid a percentage of PROLIFT sales).[193] The more concerning details of this study appeared in the full manuscript, published two months later.

(Fatton, et al,):

In **November of 2006**, the full manuscript of the Fatton, et al., PROLIFT IUGA poster presentation was published.[194] Iin this publication, the authors revealed that their complications and anatomic results were limited to 3 months post-implant. This manuscript disclosed concerning facts not presented in the IUGA poster. The de novo dyspareunia rate was 13% (higher than the 8% previously reported in Ethicon's French TVM study). Although the poster reported a 4.7% incidence of mesh extrusion, the manuscript disclosed that another 2.8% of patients had probable mesh extrusion.[195] Hence, a more accurate reporting of the mesh extrusion rate was 7.5% at 3 months. Whereas the Ethicon-sponsored French TVM study could not report on untreated compartment failure (Patients received Total TVM procedure), this study could and did report on untreated compartment failure (approximately 50% of patients received PROLIFT kits other than Total PROLIFT).
At 3 months, 39% of patients undergoing posterior PROLIFT had evidence of untreated compartment failure. At 3 months, 40% of patients undergoing anterior PROLIFT had evidence of untreated compartment failure.[196] The authors acknowledged that a risk of isolated anterior or posterior PROLIFT "is to provide a de novo prolapse in a compartment that previously appeared well-supported." These findings of approximately 40% incidence of untreated compartment failure would later be validated in a prospective study by Withagen, et al. Interestingly, the authors eventually added the native tissue repair known as sacrospinous colpopexy to their anterior PROLIFT surgeries to protect against untreated compartment failure. The reported success rate was 5 out of 5 patients treated with this combination. Although the authors described the de novo dyspareunia rate to be substantially less than 20%

---

193 ETH.10963 AND ADDITIONAL PAGES

194 Fatton B, Amblard J, Debodinance P, Cosson M, Jacquetin B. Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (ProliftTM technique) - a case series multicentric study. Int Urogynecol J 2007; 18: 743-752.

195 2.7% have patients developed granulation tissue.

196 Fatton B, Amblard J, Debodinance P, Cosson M, Jacquetin B. Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (ProliftTM technique) - a case series multicentric study. Int Urogynecol J 2007; 18: 750. Table 7. Five of the 20 anterior PROLIFT patients underwent sacrospinous colpopexy and were excluded from the denominator of this calculation.

(anterior) and 63% (posterior), described by Milani, et al., (self-tailored PROLENE mesh), they failed to consider the obvious fact that Milani, et al., measured dyspareunia at a mean of 17 months and not 3 months. Both mesh contraction and extrusion increases over time.[197] The authors of this PROLIFT study did at least acknowledge, "Nevertheless, as recommended by some experts [26], a direct comparison between totally free, tension-free and secured mesh must be realized to allow an objective argument."

In this first presentation of data on the use of the PROLIFT kit, more than one year since PROLIFT was released to the U.S. market, the authors ended their discussion with the following comments: "Various issues need to be addressed in future studies including a prospective randomised trial comparing the anatomical and functional outcomes of mesh reinforcement and site specific fascial repair alone. In addition, future studies should include longer follow-up to assess procedure efficacy and to prove a low rate of long-term complications. Prospective evaluation of the functional outcome is necessary to support the widespread use of this technique and to recommend it to young women with weakened tissues."

In summary, **between September and November of 2006**, a group comprised of the inventor of the prototype PROLIFT surgery and his French colleagues who assisted in the refinement of the surgery, a group with over five years of experience with the TVM procedure, published the first outcome data on the actual PROLIFT device. At the time of this publication the PROLIFT device had already been in use for over a year. This publication further validated the already concerning data on the PROLIFT procedure and device. It provided further evidence of high extrusion rates, high de novo dyspareunia rates and very high overall failure rates and provided no evidence of efficacy comparable to traditional surgeries. These investigators, financially and emotionally biased in favor of PROLIFT, continued to indicate the need for prospective randomized trials, a recommendation that had been in place since 2005. The fact that expert surgeons with five years of experience with the TVM procedure were unable to improve on the already concerning results once again drew into question the marketing of the PROLIFT device to the general gynecologist and urologist. In disregard of the still growing pool of worrisome data on the TVM procedure and PROLIFT device, Ethicon continued to market the still experimental PROLIFT device, hold the majority of its prospective data in strict confidence, and failed to initiate any randomized controlled trials. The continued use of PROLIFT by surgeons in the U.S. and abroad represented a rapidly growing clinical trial, a trial that both surgeons and patients were unknowingly participant.

(Carey, et al.):

[197] Discussed and evidenced in the material defect sections of this monograph.

In **February of 2007**, Carey, et al., published their one-year prospective observational study on women undergoing a modified TVM procedure.[198] Ninety-five women underwent treatment of anterior and posterior prolapse with armed GYNEMESH that was placed on top of the pelvic muscles rather than penetrating them. The PROLIFT tools and blind passes had been eliminated. Anatomic success at one year, POP-Q of Stage 0 or 1, was 85%. This is better than that reported in Ethicon's 1-year French TVM report. Mesh exposure (extrusion) was reported to be 4.2%. This is remarkably lower than that reported in Ethicon's 1-year French and U.S. TVM reports (10-14%). One might be surprised that this report, a report by an Ethicon paid consultant, demonstrating a way to increase efficacy and complications, did not cause Ethicon to update the PROLIFT labeling or make public comment. More shocking, however, is the fact that Ethicon had purchased the patent on this method from Dr. Carey in 2004, and Ethicon had believed, since 2005, that this method could reduce complications associated with PROLIFT.[199]

(Tunn, et al.):

In **March of 2007**, Tunn, et al., investigators that earlier noted a concerns for published data demonstrating early POP recurrences following surgery with the TVM method, published their prospective observational ultrasound assessment of women undergoing transvaginal mesh implantation with armed mesh kits, Anterior and Posterior PROLIFT, and Perigee and Apogee (American Medical Systems).[200] The authors stated "we conducted the present study to determine sonographically the postoperative size of the mesh implant, to compare it with the size of the implanted mesh, and to evaluate whether full support of the anterior or posterior compartment is achieved." Ultrasounds were performed six weeks after implantation. Tunn found a 61% shrinkage of the PROLIFT Anterior and a 65% shrinkage of the PROLIFT Posterior. The mean mesh lengths at 6 weeks were 3.0 and 3.2 cm (anterior and posterior PROLIFT). The authors noted that, at six weeks post implantation, PROLIFT supported only 42.9% of the anterior vagina and 50.3% of the posterior vagina. Ultrasound images of the anterior compartment at 6 weeks post implantation demonstrated the contracted and thickened mesh to reside predominantly under the distal bladder and bladder neck.[201] The PROLIFT labels describe fixation of the mesh with sutures to be optional and that such may aid in proper placement.[202] Indeed, 40-50% of physicians were placing such sutures to "keep the mesh flat."[203] Tunn, et al.,

---

198 Carey M, Slack M, Higgs P, Wynn-Williams M, Cornish A. Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG 2008;115:391–397.

199 ETH.MESH.07902335. PROJECT INITIATION PROPOSAL

200 Tunn, R., A. Picot, J. Marschke, and A. Gauruder-Burmester. "Sonomorphological Evaluation of Polypropylene Mesh Implants after Vaginal Mesh Repair in Women with Cystocele or Rectocele." .Ultrasound in Obstetrics and Gynecology Ultrasound Obstet Gynecol</i> 29.4 (2007): 449-52.

201 Tunn, R., A. Picot, J. Marschke, and A. Gauruder-Burmester. "Sonomorphological Evaluation of Polypropylene Mesh Implants after Vaginal Mesh Repair in Women with Cystocele or Rectocele." .Ultrasound in Obstetrics and Gynecology Ultrasound Obstet Gynecol. 29.4 (2007): Figure 2.

202 ETH.MESH.03960104

203 ETH-19624, Prolift Forums and Round ≥ 11-16-2005; Heading of Additional Sutures.

included this optional step, "All women were operated on by the same surgeon (R.T.) so that all operations were performed to the same technical standard. The technique comprised colpotomy from the bladder neck (cystocele) or perineum (rectocele) to the apex of the vagina without resection of vaginal wall tissue and fixation of all meshes with non-permanent sutures (Vicryl) on both sides of the apex of the vagina (muscular layer of the vaginal wall) to avoid early shrinkage of the mesh during wound healing. The posterior meshes were additionally attached on the right and left sides at the level of the proximal deep part of the perineum for the same reason." However, based on their ultrasound findings, the authors concluded that such suture fixation was helpful, "However, correlation of the total vaginal length and the length of the implanted mesh (minus the length of the urethra (anterior) and the perineum (posterior)) showed that the non-permanent stitches for additional mesh fixation do not influence the mesh position." Additionally, these sutures did not prevent the ultrasound appearance of mesh "concertina-like folding in vivo." The authors concluded, **"The observed discrepancy between the mesh length at surgery and the sonographically measured length at follow-up urgently requires further evaluation and should be taken into consideration in the further development of new products." The findings of this prospective study identified a rather alarming explanation for the concerning incidence of POP recurrence and complications reported in both the retrospective data and prospective Ethicon TVM data. In complete disregard of these findings, Ethicon neither pulled PROLIFT off the market, nor initiated clinical trials or its own ultrasound trials to validate or invalidate these findings.**

(Sivaslioglu, et al.):

In **March of 2007**, a randomized comparison of polypropylene mesh surgery with site-specific surgery in the treatment of cystocele, Sivaslioglu et al., was published. This study randomized 45 patients to site-specific native tissue repair (e.g. paravaginal repair) and 45 patients to a four-armed transobturator Parietene Mesh (Sofradim). This study compared anatomic success (POP-Q of 0 or 1). Although this study found a higher anatomic success rate associated with the mesh repair (91 versus 72% at one year), there was no significant difference in quality of life outcomes. The difference in anatomic success cannot be generalized to native tissue repair of the anterior compartment. As noted, Sivaslioglu opted for site-specific native tissue repair, a type of native tissue repair shown to be less effective than the traditional anterior colporrhaphy.[204] Hence, the findings of this study were that the four-armed Pareitene Mesh repair outperformed the site-specific anterior repair with regard to POP-Q score at 12 months. This study in no way evidences a symptomatic benefit. Furthermore, this study makes no comparison between the 4-armed Parietene anterior mesh and the traditional, more efficacious (versus site specific repair) anterior colporrhaphy. As

[204] Chmielewski L, Walters MD, Weber AM, et al. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol 2011;205:69.e1-8**.** Abramov Y et al. Site-specific rectocele repair compared with standard posterior colporrhaphy. Obstet Gynecol 2005; 105: 314-318.

a final note, this study uses a mesh that is different than PROLIFT and does not utilize the guides, cannula, or retrieval instruments of the PROLIFT device.

(Hiltunen, et al.):

In **August of 2007,** Hiltunen and Nieminen published their first of three articles on their randomized controlled trial of 202 women undergoing either the traditional native tissue anterior colporrhaphy or that same anterior colporrhaphy reinforced by a 4-armed piece of mesh.[205] This mesh, Parietene (Sofradim Co.) was lighter than the GYNEMESH PS being used by the TVM group and PROLIFT and had pores reported by the authors to be 1.5 x 1.7 mm. Unlike PROLIFT and other armed mesh kits, these investigators did not pull the arms through the obturator muscle. The arms were simply placed alongside the muscles. When evaluating this article, there are multiple key points that need to be considered:

- This article does not compare transvaginal mesh to traditional native tissue surgery. It compares a surgery that combines native tissue surgery with a self tailored non-muscle-penetrating mesh surgery to native tissue surgery alone.
- A very common complication of PROLIFT and other vaginal mesh surgeries, untreated compartment failure and re-operation for such cannot be assessed. The majority of patients (70%) underwent concomitant native tissue repair in the posterior compartment and 35% underwent surgical treatment at the apex, leaving few compartments completely untreated.
- The mesh used by these investigators was different than that of PROLIFT (lighter and perhaps less nano-porous).
- The investigators did not use a validated questionnaire for symptoms.
- There was no assessment of dyspareunia.

The authors utilized a 12-month POP-Q of stage 2 or greater to define anatomic failure. Based on this criterion, they found a significantly higher failure rate amongst those women whose anterior colporrhaphy was not reinforced with mesh (38.5 vs. 6.7%). They calculated that 4 women would need to have anterior colporrhaphy reinforced with Perietene in order to prevent one case of stage 2 POP, a stage that the authors state is most often asymptomatic.[206] Furthermore, the authors found that the Perietene mesh reinforcement did not resolve the patient's symptoms more frequently than the traditional technique. The authors reported mesh exposure (extrusion) in 17.3% of women. Even though all patients were treated, resolution was only noted in 33% of mesh exposures. Resolution of mesh exposure was only noted in

---

[205] Hiltunen R et al. Low-weight polypropylene mesh for anterior vaginal wall prolapse: a randomized controlled trial. Obstet Gynecol 2007; 110 (2 Pt 2): 455-462.

[206] These investigators did not disclose the POP-Q scores of the women who met the failure definition. However, they did report that the mean POP-Q of the entire native tissue group at 12 months. Point Aa was -1.5 +/-1.4. Point Ba was -1.6 +/- 1.5. The simple math tells us that, within 2 standard deviations of the mean, not a single patient had prolapse beyond the hymenal ring. Five percent of 97 women would fall outside this range, 2.5% above and 25% below. Hence, less than 3 women in the no-mesh group were beyond the hymenal ring. Those 1 or 2 women beyond the hymenal ring may very well have still been POP-Q stage 2. "Despite better anatomic results, the mesh tech- nique in our hands did not resolve patents' symptoms more frequently than the traditional technique. This reflects the fact that the majority of stage II recur- rences are asymptomatic."

25% of those treated with estrogen cream. Those treated with surgical resection of the exposure and or closure did not fare much better. Only 36% resolved. Mesh reinforcement resulted in a significantly higher incidence of de novo stress urinary incontinence (23% vs. 10%, p=0.2). Although the authors state that there was not a significant difference in the re-operation rate between the groups, this statement is misleading. The authors reported a 4.8% incidence of re-operation in the mesh group. However, curiously, they opted to exclude the 14 women who had resections and closures for mesh complications. Inclusion of these women raised the reoperation or re-intervention rate to 18% versus 6.2% found in the anterior colporrhaphy group. The author's final paragraph states, "We conclude that reinforcing anterior colporrhaphy with tailored low-weight polypropylene mesh reduces the recurrence rate. Mesh exposure remains a problem with our technique, and the stress urinary incontinence rate is higher with the mesh technique and should be taken into account when counseling a patient." Although the later portion of this statement is candid, the first part is misleading.

This study does not demonstrate that reinforcing anterior colporrhaphy with tailored low-weight polypropylene mesh reduces the recurrence rate. It shows that it decreased the recurrence of stage 2 POP, the stage of POP the authors report is typically asymptomatic. Hence, according to these authors and their findings, A surgeon would need to treat 4 patients with Parietene mesh reinforcement to prevent one asymptomatic recurrence. In practice, the surgeon can expect to see 17% of patients develop mesh extrusion that will most likely fail treatment, a doubling of patients that experience stress urinary incontinence, and experience significantly longer and bloodier operations.

(Neiminen, et al.):

In **April of 2008,** Neiminen and Hiltunen published a 24 month follow-up of their 2007 study comparing anterior colporrhaphy to anterior colporrhaphy reinforced with Parietene, **Symptom resolution and sexual function after anterior vaginal wall repair with or without polypropylene mesh.**[207] Please see my discussion of the first year of this study for details on the methods and materials and analytic concerns associated with the 12 month data. The authors state that the purpose of this 24 month follow-up was, "To evaluate whether symptom resolution and sexual function is better after reinforcement with polypropylene mesh than with traditional anterior repair." Between 12 and 24 months, the failure rate of the mesh-reinforced group increased by 4.7%, compared to only a 2.5% increase in the no-mesh group. This was not commented on or evaluated for significance, although the evaluation of efficacy was not the objective of this 24 month follow-up study. When evaluating the

[207] Nieminen, Kari, Reijo Hiltunen, Eila Heiskanen, Teuvo Takala, Kirsti Niemi, Mauri Merikari, and Pentti K. Heinonen. "Symptom Resolution and Sexual Function after Anterior Vaginal Wall Repair with or without Polypropylene Mesh." International Urogynecology Journal Int Urogynecol J. 19.12 (2008): 1611-616.

findings of this study, several key points covered in my discussion of their 12-month study remain important:

- This article does not compare transvaginal mesh to traditional native tissue surgery. It compares a surgery that combines native tissue surgery with a self tailored non-muscle-penetrating mesh surgery to native tissue surgery alone.
- The majority of patients (70%) underwent concomitant native tissue repair in the posterior compartment and 35% underwent surgical treatment at the apex, leaving few compartments completely untreated. Hence, comparisons of sexual function and symptoms do not relevant to anterior colporraphy vs. Parietene reinforced anterior colporrhaphy, but relate to these two methods combined with other surgeries.
- The mesh used by these investigators was different than that of PROLIFT (lighter and perhaps less nano-porous).
- The investigators did not use a validated questionnaire for symptoms or sexual function. Hence it is not possible to draw meaningful conclusions from statistical analysis of this data.

Although the authors note a significant difference between the percentages of women with dyspareunia at 24 months, this is of little meaning for multiple reasons. First, neither group demonstrated a significant increase or decrease in dyspareunia. So, if a validated questionnaire had been used, the finding could have been stated as: Between two groups that did not experience any increase in dyspareunia, the post-operative mesh group had significantly less members with dyspareunia; However, based on available literature, many if not the majority of women in this mesh group represent women with new onset dyspareunia.[208] Secondly, the authors did not collect (or at least did not report on) the incidence of de novo dyspareunia. When tracking sexual function, most surgeons and others skilled in the art would report on the incidence of de novo dyspareunia. It is neither fair, nor ethical, to trade one woman with known and treatable dyspareunia for another woman with new and perhaps untreatable dyspareunia. It is also worth noting that the 37% of the mesh group reported that their vagina was not the appropriate size for intercourse compared to 19% in the no-mesh group. Although the authors suggest that this was associated with their technique, a technique they believed decreased dyspareunia, they did not consider the fact that contracted non-elastic mesh prevents the vagina from conforming to the shape of the penis.

Although the authors acknowledge that the mesh reinforcement did not confer a significant benefit in overall symptoms, they reported that mesh reinforcement resulted in significantly fewer women with bulge symptoms. Although the scores for bulge symptoms do appear in the table, the authors do not discuss the fact that, using their non-validated scoring system of 1-5, both groups has significant improvements in bulge symptoms with identical p scores (.000), and the mean scores of the groups

[208] The authors cite studies demonstrating a high rate of de novo dyspareunia following mesh implantation. De Tayrac et al study cited by authors found 12.5% de novo dyspareunia. Dwyer found that almost half of the dyspareunia was de novo.

were 1.4 and 1.2. The authors also fail to comment on the fact that their non validated scoring system found approximately 25% of patients with Grade 0 POP (no prolapse) to have prolapse related symptoms.[209]

Mesh extrusion increased from 17% to 19.5%. Even though all of the mesh extrusions noted in the 12-month report were treated, 39% were persistent at 24 months.

The authors excluded from their calculations all women who underwent surgery for recurrent POP, yet opted to treat them as missing data. The authors used the Last Observation Carried Forward Method to account for all missing data, including those lost to follow-up. This method takes the POP-Q and complications at the last observation (before patient lost to follow-up or had repeat POP surgery) and carries it forward. As recurrences (failures) never go away but patients but new ones occur over time, the LOCF method is biased toward decreasing the calculated failure and complication rates (POP symptoms).

In summary, this study provided no meaningful data with regard to differences in sexual or functional outcome between a group of women undergoing anterior colporrhaphy, versus a group of women undergoing anterior colporrhaphy with Parietene mesh reinforcement without trocars or muscle penetration. In a comparison of theses unique groups combined with additional surgeries, this study did show an increase in mesh extrusion and demonstrates that almost 40% of mesh extrusions failed to respond to treatment and persisted at two years. This study creates even further concern with regard to the worrisome findings of their one-year report. There is no evident functional benefit associated with this unique mesh surgery, yet there a clear concern for novel and persistent morbidly.

(Shek, et al.):

In **June of 2008**, Shek, et al., published the first of their two studies utilizing ultrasound to assess the short to medium term results of the TVM type procedure, **Transobturator mesh for cystocele repair: a short- to medium-term follow-up using 3D/4D ultrasound.**[210] This was a retrospective surgical audit of women who had undergone the implantation of an armed transobturator mesh, similar to PROLIFT (Perigee, American Medical Systems). Unlike the method of Tunn, et al., Shek did not perform a baseline ultrasound at time of implantation. A single ultrasound was performed at mean 10 months post-implantation. However, other investigators have documented the pre-implantation length of Perigee to be 9.5 cm.[211] At a mean of 10 months, the post implantation mesh length ranged from 0.9 cm to 3.7 cm, with a

---

209 See table 2 of study.

210 Shek, K. L., H. P. Dietz, A. Rane, and S. Balakrishnan. "Transobturator Mesh for Cystocele Repair: A Short- to Medium-term Follow-up Using 3D/4D Ultrasound." .Ultrasound in Obstetrics and Gynecology Ultrasound Obstet Gynecol</i> 32.1 (2008): 82-86.

211 Tunn, R., A. Picot, J. Marschke, and A. Gauruder-Burmester. "Sonomorphological Evaluation of Polypropylene Mesh Implants after Vaginal Mesh Repair in Women with Cystocele or Rectocele." .Ultrasound in Obstetrics and Gynecology Ultrasound Obstet Gynecol</i> 29.4 (2007)

mean post implantation length of 2.1 cm. This represents a 78% reduction in length.[212] As implemented by Tunn, et al., Shek also implemented the option of suturing of the mesh and, likewise, found no benefit; "Postoperatively, the Perigee mesh seems to cover a smaller area than anticipated. It remains to be seen whether this effect can be alleviated by modifications in technique, such as more permanent anchoring of the mesh to the bladder neck and vault."[213] Shek concluded, "Future research should focus on causes and mechanisms of suspension failure in order to optimize the design of mesh implants." **Even after the findings of Shek validated the concerning findings of Tunn, et al., and also recommended further research focusing on the causes of failure, Ethicon left PROLIFT on the market and initiated no such studies or trials.**

(Caquant, et al.):

In **August of 2008**, approximately three years since the presentation of their ICS abstract with "worrying" data, these same authors published their full manuscript, **Safety of Trans Vaginal Mesh procedure: Retrospective study of 684 patients**.[214] Whereas their abstract had disclosed a 6.7% incidence of mesh extrusion, the full manuscript provided evidence of mesh extrusion in 11.3% of women.[215] The majority required surgical excision. The authors described the incidence of extrusion to be high. Whereas the abstract had reported a 5.3% incidence of recurrent POP, the full manuscript documents a higher rate of recurrent POP, 6.9%. Although not described in their abstract presented three years earlier, the investigators now report an 11.7% incidence of mesh retraction (contraction). The investigator found the incidence of retraction in the anterior compartment to be highest at 17.6% and identified a significant relationship between retraction and recurrent POP. The authors concluded that "the present study shows a relatively high incidence of late post-surgical complications" and "symptomatic prosthetic retractions may be of handicap with pelvic pain, dyspareunia, dyschesia." The concerning findings of recurrences and complications, findings from data first analyzed in 2005, necessitated a discontinuation of the marketing of the experimental PROLIFT device with the initiation of a voluntary and consented randomized clinical trial. Ethicon did neither.

(Cosson, et al. & Dede,t et al.):

Between **September 13th and 17th of 2008**, Dr. Cosson and multiple other investigators from Ethicon's French TVM study (including investigators and authors of the 2005 TVM papers) published a series of abstracts on the TVM and PROLIFT

---

[212] If the mean immediate post implantation Perigee length of Tunn et al (6.4 cm) is substituted for the naïve Perigee length, Shek et al data would still demonstrate a 68% shrinkage by 10 months.

[213] Shek, K. L., H. P. Dietz, A. Rane, and S. Balakrishnan. "Transobturator Mesh for Cystocele Repair: A Short- to Medium-term Follow-up Using 3D/4D Ultrasound." .Ultrasound in Obstetrics and Gynecology Ultrasound Obstet Gynecol</i> 32.1 (2008): 86.

[214] Caquant, Fréderic, Pierre Collinet, Philippe Debodinance, Juan Berrocal, Olivier Garbin, Claude Rosenthal, Henri Clave, Richard Villet, Bernard Jacquetin, and Michel Cosson. "Safety of Trans Vaginal Mesh Procedure: Retrospective Study of 684 Patients." .Journal of Obstetrics and Gynaecology Research</i> 34.4 (2008): 449-56

[215] Authors grouped mesh extrusion and granulaton tissue together as the later is an indication of the former.

device. These abstracts were presented at the 33rd Annual IUGA Meeting in Taipei, Taiwan. The first two of these abstracts involved retrospective data on the TVM procedure and the third abstract included three year data from the Ethicon French prospective observational study.

(Cosson, et al.):

Preservation Of Uterus When Treating Prolapse By PROLIFT TM Does Not Significantly Reduce Risk Of Early Post Surgical Complications And Failures.[216] This was a retrospective review of 217 women who underwent the PROLIFT implantation by the some of the most experienced TVM surgeons in the world. Patients were divided into three groups for analysis: Previous Hysterectomy, Concomitant Hysterectomy, and Uterine Preservation. Ten weeks post TVM procedure, recurrent POP was identified in 17% of the concurrent hysterectomy group and 8% of the uterine conservation group. This difference in mesh extrusion rates was found to be non-significant. Hence, the previous recommendation of Cosson and Lucot that "the uterus must be preserved" was not supported by the statistical analysis**. The authors concluded, "This underlines that keeping the uterus seems interesting but needs to be strictly evaluated by prospective comparative studies." Now, over three years since the initial marketing of PROLIFT in the United States, the dangers of concomitant hysterectomy have still not been appropriately evaluated and surgeons continue to, unknowingly, experiment with their patients. Further, the finding of a 17% recurrence rate only ten weeks post the PROLIFT implantation by some of the most experienced PROLIFT surgeons in the world, once again, creates great concerned for the efficacy of the PROLIFT procedure in the hands of general gynecologists and urologists.**

(Dedet, et al.):

Transvaginal Repair Of Genital Prolapse By The PROLIFT Technique: Outcome One Year After Surgery.[217] This was a retrospective review of 217 women who underwent the PROLIFT implantation by the some of the most experienced TVM surgeons in the world. At one year, the recurrence rate was between 6% and 7% (6% for cystocele recurrence). However, the authors do not disclose the definition of recurrence or if they included the untreated compartments. Mesh retraction was noted to be in 20% of women. Mesh exposure was reported in 6%. However, the authors do not disclose the treatment of mesh extrusions that may have occurred prior to the one-year evaluation. Although the authors conclude that "PROLIFT repair appears to be

[216] Cosson M, Jean Charles C, Debodinance P, Lucot JP, Rubod C, Boukerrou M., Preservation Of Uterus When Treating Prolapse By Prolift TM Does Not Significantly Reduce Risk Of Early Post Surgical Complications And Failures. Int Urogynecol J (2008) 19 (Suppl 1):S92.

[217] Dedet B, Rubod C, Boukerrou M1, Debodinance P, Cosson M., Transvaginal Repair Of Genital Prolapse By The Prolift Technique: Outcome One Year After Surgery. Int Urogynecol J (2008) 19 (Suppl 1):S97.

a good and safe technique to repair pelvic organ prolapse," this is a retrospective study and lacks a control group and some of these same investigators had just reported a 17% incidence of recurrence ten weeks following PROLIFT. Here, there is a reported a 20% incidence of retraction (contraction) without evaluation of sexual function, and some of these same investigators had already reported an 8% incidence of de novo dyspareunia in a prospective study. The statement, "PROLIFT repair appears to be a good and safe technique to repair pelvic organ prolapse," is not supported by evidence. Indeed, the final statement made in their conclusion states "Anatomical and functional results must be assessed with a long-term follow-up to confirm the effectiveness and safety of the procedure."

(Cosson. et al.):

Prospective clinical assessment of the Total TransVaginal Mesh (TVM) technique for treatment of Pelvic Organ Prolapse - 3 year results.[218] This represents the first public disclosure of the Ethicon sponsored TVM study. "The objective of the study was to evaluate the long-term safety and effectiveness of the Trans-Vaginal Mesh (TVM) technique for anterior, posterior and vault prolapse repair." The authors reported an 18.8% recurrence rate (upper C.I. 27.2%). They also reported a decrease in moderate to severe vaginal retraction from 12.6 to 9.4%. Of additional concern, the rate of de novo dyspareunia increased from 8% to 15.4%.[219] The 35% reduction in sexual activity noted at one year had not improved.[220] Additionally, the incidence of mesh extrusion had increased from the 10% noted at one year to 15% at three years. Mesh extrusion persisted in 71% of patients not undergoing surgical excision.[221] Regardless of the mode of management, the overall persistent mesh erosion rate was 46% (5/13). Strangely, the authors of this Ethicon sponsored study and manuscript conclude, "These results demonstrate that TVM provides stable anatomical and QOL improvements through to 3 years with a low rate of mesh exposure and complications." Several of these authors had previously published studies that include the

---

[218] Cosson M, Rosenthal C, Debodinance P, Clave H, Berrocal J, Jacquetin B. Prospective clinical assessment of the Total TransVaginal Mesh (TVM) technique for treatment of Pelvic Organ Prolapse - 3 year results. Int Urogynecol J (2008) 19 (Suppl 1):S106

[219] 2 patients with persistent de novo dyspareunia (from 1 yr data), 2 patients that developed de novo dyspareunia between 1 and 3 years, 1 patient that had resolution of pre-existing dyspareunia at 1 year and developed new dyspareunia by 3 years, and one case of "intermittent" dyspareunia. 39 Patients were sexually active.

[220] 61 women were sexually active prior to TVM. 40 were sexually active at 1 year after implant. 39 are sexually active at 3 years.

[221] 13 women suffered mesh extrusion. A total of six had undergone excision (5 at one year and one now). If we allow that excisions resulted in cure, 5 of the 7 patients not excised of their extrusion (71%) are with persistent mesh extrusion. Of course it is possible that excisions failed and the 46% overall persistent extrusion rate represents a combination of excisional failures and medical failures. 85 women available at 3 year follow-up

need to reduce mesh extrusion rates to below 5%.[222] The prospective data reported in this new abstract demonstrates a 15% extrusion rate. Some of these authors, just one month earlier, had stated that a mesh extrusion rate of 11.3% was high and that TVM was associated with "a relatively high incidence of post-surgical complications." These same authors, presenting the abstract for the same study, found a 5.3% POP recurrence rate "worrying."[223] The prospective data reported in this new abstract demonstrates a much higher incidence of POP recurrence and mesh extrusion rate than that previously known to these authors.[224] The conclusion of this biased group of authors, a group that contained the financially incentivized inventor, Dr. Jacquetin, provided in this manuscript (which Ethicon reserved the right to review and approve), is not supported by their findings and in contradiction to the findings and teaching published outside the supervision of Ethicon. This first reporting of mid-term data on the prototype PROLIFT surgery validates the already existing concerns for high failure and complication rates. Ethicon neither ceased the marketing of PROLIFT, nor initiated the randomized controlled trials to either further validate concerns or remove concerns.

(FDA Public Health Notice):

In **October of 2008**, FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence was issued.[225] This was a notice from the FDA to healthcare providers. The notice stated "This is to alert you to complications associated with transvaginal placement of surgical mesh to treat Pelvic Organ Prolapse (POP) and Stress Urinary Incontinence (SUI)." The notice listed many of the complications, "The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence." The notice added, "Although rare, these complications can have serious consequences." Ethicon was well aware that these same complications associated with PROLIFT were anything but rare. This data included reports of mesh exposure (extrusion) of 14-15%, de novo dyspareunia of 13%, 18-29% reoperation rates, and a 20% contraction rate and an 18% failure rate. These are not rare complications. The FDA felt compelled to notify healthcare providers of these complications it believed were rare but could have serious consequence. Ethicon knowingly opted not to inform

---

[222] Collinet, Pierre, Franck Belot, Philippe Debodinance, Edouard Ha Duc, Jean-Philippe Lucot, and Michel Cosson. "Transvaginal Mesh Technique for Pelvic Organ Prolapse Repair: Mesh Exposure Management and Risk Factors." .International Urogynecology Journal Int Urogynecol J</i> 17.4 (2005): 315-20.

[223] ETH-02351: Cosson M et al. Prolift mesh (Gynecare) for pelvic organ prolapse surgical treatment using the TVM group technique: a retrospective study of 687 patients. ICS Abstract 121, 9-2-2005

[224] Caquant, Fréderic, Pierre Collinet, Philippe Debodinance, Juan Berrocal, Olivier Garbin, Claude Rosenthal, Henri Clave, Richard Villet, Bernard Jacquetin, and Michel Cosson. "Safety of Trans Vaginal Mesh Procedure: Retrospective Study of 684 Patients." .Journal of Obstetrics and Gynaecology Research</i> 34.4 (2008): 449-56.

[225] http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm

healthcare providers of the fact that PROLIFT was associated with a high incidence of such complications.

Expert Opinion on 2008 Public Health Notice:

As a prescriber of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as the CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimony, and internal corporate documents, I state with a reasonable degree of medical and corporate certainty that:

- Surgeons expect device companies to inform them of such notices and to provide the material facts regarding the notice as it applies to its product,
- Ethicon did not update its labels or otherwise inform surgeons that these complications were not rare with the PROLIFT device, and that the failure to provide such information lead to continued use of PROLIFT and injury to women.

(Natale, et al.):

In **October of 2008,** Natale, et al., published their RCT comparing anterior compartment repair with GYNEMESH PS to Pelvicol (Porcine Dermis, CR Bard). This study utilized identically shaped armed grafts, non-fixated, that did not penetrate any of the pelvic muscles. A native tissue repair was used to treat the apex and proximal posterior compartment. Success was defined as a POP-Q of Stage 0 or 1. Validated questionnaires were used to assess quality of life as well as prolapse, incontinence, and sexual symptoms. This study reported on 190 patients at two years. Although more mesh patients met the definition of anatomic cure, the difference was not statistically significant. Ninety-five percent of GYNEMESH PS failures and 96% of Pelvicol failures were Stage 2 POP. Although 6.2% of women suffered GYNEMESH erosions, there were zero erosions in the Pelvicol group. Pelvicol resulted in a statistically significant, positive effect on sexuality, but GYNEMESH caused no significant change. Comparing postoperative data in the two groups, Pelvicol was superior to GYNEMESH ($p = 0.03$). The authors concluded "Such innovations, aimed at delivering strong tissue support while yielding low erosion rates, should be the subject for future research and should be evaluated in the context of further prospective, randomized trials."

This prospective randomized controlled trial utilizing an armed PROLIFT type mesh (GYNEMESH PS) without the blind passage of arm through muscles demonstrated a lower incidence of mesh erosion and dyspareunia than that demonstrated by Ethicon and the TVM investigators. Whereas Ethicon's prospective observational data and the TVM group's retrospective data had demonstrated a 10-15% erosion rate, this novel, non-fixated, not-penetrating use of GYNEMESH PS demonstrated a 6.2% erosion rate. Whereas treatment of TVM erosions failed 46% of the time, this study yielded a 100%

success rate. In addition, the 15% de novo dyspareunia rate demonstrated in Ethicon's 3-year French TVM data was in great excess of the dyspareunia rate reported here.[226] This is the second modification of the TVM method that demonstrated a decrease in complications. One might find it bothersome that these findings neither generated a public response from the TVM investigators, nor caused Ethicon to update its PROLIFT labels, hold PROLIFT sales, or initiate the recommended clinical trials. However, even more shocking, as discussed earlier, is the fact that Ethicon's internal documents reveal that Ethicon believed, since 2004, that it could reduce the complications of its procedure by altering the TVM method and ceasing to pass mesh arms through the muscles of the pelvis.[227]

(Blandon, et al.):

In **January of 2009**, a group of Urogynecologists from the Urogynecology Division at the Mayo Clinic (Rochester, MN), reported on their treatment of severe mesh complications.[228] Blandon, et al., performed a retrospective review of mesh complications evaluated and treated by their division. Twenty-one cases were identified, of which 86% represented mesh kits featuring the blind passage of trocars. The remaining three complications were associated with self-tailored sheet mesh or xenograft. Another interesting finding was that only 3 patients (14%) were referred by their original surgeon. The authors pointed out that this "suggests a lack of awareness of these complications by the original treating physician and the potential for under-reporting of the rate and extent of these complications due to nonrespondent/volunteer bias." The authors also noted that only 9% of patients had their original mesh implantation performed by a urogynecologist. They reported "This supports the notion that surgical technique may contribute to the development of these complications and emphasizes the need for specialized training."

Only one patient elected to be observed, and of those that allowed either conservative or medical management, only 50% noted substantial improvement. 30 percent noted no improvement or worsening of symptoms. The specialists at the Mayo clinic were unable to achieve any improvement in dyspareunia. The authors concluded, **"However, we support the notion that the new minimally invasive total mesh repairs should be done in the context of clinical trials, in which patients receive adequate informed consent and outcomes are carefully monitored." The second author, J. Gebart, disclosed a financial relationship with the manufacturer of a mesh kit, C.R. Bard.**

This report brings to light the growing concerns of expert pelvic surgeons with regard to the safety of mesh kits, the safety of mesh kits in the hands of non-

---

[226] Although Natale et al did not report the de-novo dyspareunia rate, the overall dyspareunia rate included de novo and persistant pre-existing dyspareunia was 10.4%.

[227] ETH.MESH.07902335. PROJECT INITIATION PROPOSAL

[228] Blandon RE et al. Complications from vaginally placed mesh in pelvic reconstructive surgery. Int Urogynecol J 2009; 20: 523-531.

specialists, and the growing awareness by expert pelvic surgeons that mesh kits such as PROLIFT are experimental and need to be confined to clinical trials.

(Diwadkar, et al.):

In **February of 2009,** Diwadkar, et al., reported on their meta-analysis comparing traditional vaginal surgery (native tissue), mesh kits, and sacrocolpopexy in the treatment of apical POP.[229] This was a meta-analysis of both observational studies and clinical trials with computation limited by this same fact. The authors found that mesh kits were associated with the highest overall re-operation rate. Whereas the majority of traditional vaginal surgery related complications required no surgery and responded to pharmacotherapy, the majority of mesh kit surgery complications required surgical intervention. Further, the need for a surgical treatment of a complication under general anesthesia was 1.9% for traditional vaginal surgery versus 7.2 percent for mesh kits. The authors also demonstrated concern that these ominous findings were noted, even though the studies on mesh kits had approximately half the follow-up time as those on traditional vaginal surgery. They stated, "This raises the concern that the risks of these newer procedures may be greater than their benefits. One can speculate that more recurrences and complications may be diagnosed with time, given the relatively shorter mean follow-up period in the mesh kit group." Although they offered that some of the complications and re-operations may have been secondary to the "learning curve" with mesh kits, we must remember that the experts of the TVM study (who had over 5 years of experience with TVM) had even higher rates of complications and re-operation. The authors concluded, "More long-term studies on vaginal mesh kits and clinical trials that directly compare these surgical techniques are needed to support these findings definitively." Although Ethicon was aware of this meta-analysis and the recommendation of these investigators, it neither pulled PROLIFT from the market nor initiated the recommended clinical trials.[230]

(Carey, et al.):

In **July of 2009,** Carey et al published their prospective RCT on their modification of the TVM method.[231] Sixty-nine women were randomized to anterior and posterior repair with armed GYNEMESH that was placed on top of the pelvic muscles rather than penetrating them. As previously reported, the PROLIFT tools and blind passes had been eliminated. Anatomic success at one year, POP-Q of Stage 0 or 1, was 81%. This is identical to success reported in Ethicon's 1-year French TVM report. Mesh

---

[229] Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE (2009) Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 113 (2 Pt 1):367-373

[230] In October of 2009, paid consultants of Ethicon as well as two Ethicon Employees (PH, Director of Medical Affairs, and JG, Associate Director of Clinical Development), submitted a manuscript to the International Urogynecology Journal, Int Urogynecol J (2010) 21:1455-1462, in which they cited the Diwadkar paper. , https://www.linkedin.com/in/piet-hinoul-72604a9, https://www.linkedin.com/in/judi-gauld-7434958

[231] Carey M, Higgs P, Goh J, Lim J, Leong A, Krause H, Cornish A. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomized controlled trial. BJOG 2009;116:1380–1386.

exposure (extrusion) was reported to be 5.6%. This is remarkably lower than that reported in Ethicon's 1-year French and U.S. TVM reports (10-14%). This is the second report by its paid consultant demonstrating a way to decrease complications without decreasing success. As discussed already, Ethicon's internal documents reveal that Ethicon believed, since 2004, that it could reduce the complications of its procedure by altering the TVM method and ceasing to pass mesh arms through muscles of the pelvis. Still, in disregard of its belief and the publications of its paid consultants and other investigators, Ethicon did not update the PROLIFT labeling, hold PROLIFT sales or made public comment.

(Velemir, et al.):

In **January of 2010**, a group of investigators that included the inventor of PROLIFT and two investigators from Ethicon's French TVM study, would provide alarming ultrasound and physical exam validation of severe PROLIFT contraction identified by Tunn et al.[232] This study evaluated patients implanted with the PROLIFT device between March of 2005 and August of 2006. Follow-up ultrasounds and physical examinations were performed at a mean post-implantation follow-up of 17.9 months. Recurrence of POP was defined in agreement with the original Ethicon TVM protocol. Examination of the anterior compartment found a 89% incidence of moderate to severe mesh contraction. "Patients with anterior recurrence presented significantly more often with severe anterior mesh retraction compared with patients without anterior recurrence" (62% vs. 3%, p<.001). "Patients with posterior recurrence presented significantly more often with severe posterior mesh retraction compared with patients without posterior recurrence (75% vs. 5%, P < 0.01)".[233] The authors stated "We hypothesize that, when severe mesh retraction occurs, a significant part of the bladder or rectum (usually the distal part) becomes uncovered by the mesh, allowing prolapse recurrence to occur at this unprotected part of the vaginal wall, particularly in cases of weak native tissue" and added that it is known that mesh retraction is related tissue inflammation around the mesh after implantation.[234] In an attempt to mitigate against the effects of contraction, the authors stated that they had recently modified their technique by placing sutures into the pubococcygeus muscle. Although the authors noted that most of their POP recurrences were around a gap created by the distal retraction of mesh, their ultrasound images also demonstrate the proximal retraction noted by Tunn. **The authors concluded "In conclusion, our study suggests that recurrence after TVM repair of anterior and posterior vaginal wall prolapse is associated with severe mesh retraction and loss of mesh support on the lower part of the vaginal walls". The inventor of PROLIFT and his colleagues, experts with extensive experience in the TVM method include Ethicon paid consultant B. Fatton, have now validated the concerning**

---

[232] Velemir L et al. Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study. Ultrasound Obstet Gynecol 2010; 35: 474-480.

[233] Velemir L et al. Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study. Ultrasound Obstet Gynecol 2010; 35: 477-478

[234] Velemir L et al. Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study. Ultrasound Obstet Gynecol 2010; 35: 474

2007 findings of Tunn et al and 2008 findings of Shek et al. They have also identified loss of support in the distal vagina and shown a significant relationship between contraction and failure. Yet, still, Ethicon has chosen to leave PROLIFT on the market and refrains from initiating clinical trials.

(Cochrane, Maher, et al.):

In **April of 2010**, the independent Cochrane Incontinence Group published its an update on its 2007 systematic review of the literature, Surgical management of pelvic organ prolapse in women.[235] The group relied strictly on randomized controlled trials and reported that "No data exist on efficacy or otherwise of polypropylene mesh in the posterior vaginal compartment". Although the group reported that standard anterior colporrhaphy was associated with a higher failure "on examination" the added that they found no difference in subjective outcomes".
The group provided caution, "Data relating to polypropylene mesh overlay were extracted from conference abstracts without any peer reviewed manuscripts available and should be interpreted with caution". The Cochrane group herein drew attention to the concerning experimental nature of PROLIFT. The group could find no level one evidence to support the use of mesh in the posterior compartment. The group could only find abstracts of RCTs to suggest that there was an anatomic but not a symptomatic benefit in the anterior compartment. Yet, the level 2 literature consistently provided concerning data with regard to mesh related complications. Ethicon did not respond with the initiation of a RCT to support the use of PROLIFT.

(Jacquetin, et al., Ethicon's 3-year French TVM data):

In **August of 2010**, approximately 2 years after the abstract was presented, the 3-year data Ethicon French TVM data was published as a complete manuscript, Total Transvaginal Mesh (TVM) Technique For Treatment Of Pelvic Organ Prolapse : A 3-Year Prospective Follow-Up Study.[236] The authors reported a 20.2% POP recurrence rate (28.5% at 90% confidence interval).[237] This rate was based on the most favorable calculation of missing data, Last Observation Carried Forward (LOCF). This method takes the POP-Q at the last observation (before patient lost to follow-up) and carries it forward. As recurrences (failures) never go away but patients who had not failed at 1 year certainly fail later on, the LOCF method is biased toward decreasing the calculated failure rate. The study protocol called for two methods of dealing with missing data, LOCF and assuming missing data represented a recurrence. The LOCF method of dealing with missing data does not utilize statistical principles, generally

---

[235] Maher C, Feiner B, Baessler K, Glazener CMA. Surgical management of pelvic organ prolapse in women. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD004014. DOI: 10.1002/14651858.CD004014.pub4.

[236] Jacquetin, Bernard, Brigitte Fatton, Claude Rosenthal, Henri Clavé, Philippe Debodinance, Piet Hinoul, Judi Gauld, Olivier Garbin, Juan Berrocal, Richard Villet, Delphine Salet Lizée, and Michel Cosson. "Total Transvaginal Mesh (TVM) Technique for Treatment of Pelvic Organ Prolapse: A 3-year Prospective Follow-up Study." .International Urogynecology Journal Int Urogynecol J</i> 21.12 (2010): 1455-462.

[237] The authors state in their discussion that the anatomic success rate was 81.2% but this is not supported by their data, calculation, or reports throughout this manuscript of 20.2 percent failure.

results in misleading conclusions, and is not advocated as a primary analytic strategy.[238] Of the two methods allowed by Ethicon's TVM protocol, the later method is the most conservative method when evaluating for complications and herein resulted in a recurrence rate of 24.4% (33% at 90% confidence interval). Although this data was presented in a table, the grave significance of such was not discussed. The range of the upper limit of the confidence interval was 28.5 to 33% (reflecting the two different methods of dealing with missing data). As per the Confidential Statistical Analysis Plan "The study will be deemed a success providing the upper 90% two-tailed confidence interval (same as the tail on a one tail 95% CI) does not exceed 20%. Otherwise, the study will be a failure, as it will not show that the prolapse rate is <20%".[239] As would be expected, as recurrences to not improve, the TVM study that was a failure at one year remains a failure at 3 years. The authors also provided in this manuscript misleading information with regard to mesh extrusion. They stated that, "after three years, 4.7% asymptomatic extrusions remained present." However, the authors clearly indicate that there are have been a total of 13 mesh extrusion and that there are 4 ongoing cases which are asymptomatic. Hence, after three years, 30.8% of mesh extrusion remained present (4/13) even though more than half of patients with mesh extrusions have undergone surgery for such.[240] The authors corrected their previous (abstract) claim that there had been an improvement in mesh retraction from the one-year data (12.6%) and herein report that the number has not changed. The do however change the description from "moderate-severe retraction" to **"moderate to severe vaginal stiffness (loss of elasticity)" and report that it is "always associated with mesh contraction". They further stated "We deemed the increased fibrosis responsible for the loss of elasticity of the vaginal walls".** The authors once again described a dramatic reduction in sexual activity (41% reduction) and reported that this finding was "concerning" and "warrants future studies specifically addressing the impact of vaginal mesh repairs on sexual function.[241] As what seems to have become a pattern, the authors once again provide misleading statistics. They state "There were five out of 57 patients who reported de novo dyspareunia (8.8%)." However, only 39 women are sexually active. Hence, the appropriate calculation of dyspareunia is 5/39 or 12.8% (and calculations based on their abstract narrative demonstrate a higher number, 6/39 or 15.3%). The authors again misrepresent the data in their discussion of the re-operation rate; "The total re-intervention rate of 12/90 (13.3%) is thus made up by three operations for recurrence of prolapse, eight interventions for mesh exposure and one procedure to

---

[238] James D. Dziuraa, Lori A. Posta, Qing Zhaob, Zhixuan Fub, ,and Peter Peduzzib. Strategies for dealing with Missing data in clinical trials: From design to Analysis. Yale Journal Of Biology And Medicine 86 (2013), Pp.356. James Carpenter. Statistical modelling with missing data using multiple imputation.Lecture 2: Ad-hoc methods and introduction to multiple imputation. Pg.5-6

[239] ETH.MESH.00401472

[240] By stating that only 4.7% of mesh extrusions remained present, the authors mislead the reader to believe that 95.3% of mesh extrusions resolved. The 4.7% however represents the number of remaining and asymptomatic mesh extrusion as a fraction of the total study population and not as a fraction of those that had a mesh extrusion.

[241] Jacquetin, Bernard, Brigitte Fatton, Claude Rosenthal, Henri Clavé, Philippe Debodinance, Piet Hinoul, Judi Gauld, Olivier Garbin, Juan Berrocal, Richard Villet, Delphine Salet Lizée, and Michel Cosson. "Total Transvaginal Mesh (TVM) Technique for Treatment of Pelvic Organ Prolapse: A 3-year Prospective Follow-up Study." .International Urogynecology Journal Int Urogynecol J</i> 21.12 (2010): 1461

treat the vesicovaginal fistula". However, in their results they describe three more surgeries (one for evacuation of a hematoma, on to treat urinary retention, and on for mesh impinging on the trigone). The correct surgical re-intervention rate is therefore 16.6%. The authors offered a comparison to the 8.5% reoperation rate reported by Diwadkar et al suggesting that fully standardized mesh kits may be associated with lower reoperation rates for complications. However, the authors neglect to disclose the meta-analysis of Diwadkar comparing mesh kits to traditional vaginal vault suspensions found that mesh kits were associated with the highest incidence of reoperation. Additionally, as the mean follow-up period for the mesh patients was only approximately half that of the traditional vaginal surgery group, Diwadkar stated "This raises the concern that the risks of these newer procedures may be greater than their benefits. One can speculate that more recurrences and complications may be diagnosed with time, given the relatively shorter mean follow-up period in the mesh kit group". Furthermore, the authors of this TVM paper misstate that the follow-up of Diwadkar's mesh group was 26 months. The follow-up was 17 months compared to 32 months in the traditional vaginal surgery group.

The TVM authors acknowledged the novel complications created by the PROLIFT device, "As we recognize that implantation of a foreign body has introduced new kinds of morbidity (e.g. mesh contraction and erosion)…" and suggested that it was time to consider new measures that include adverse event scores and re-operation for prolapse. Yet, curiously, they did not suggest that new measures should consider reoperation for complications, a uniquely elevated risk of mesh kits demonstrated by both this study and the Diwadka study cited by this study. **It should be noted that all of the authors disclosed conflicts of interest including two of the authors who were Ethicon Employees.**[242]

In summary, the published manuscript of Ethicon's 3-year French TVM data once again reminded Ethicon that it had failed to meet it's predefined success criteria, demonstrated a failure rate well beyond the predefined 95% CI of 20% (at least 28%), and further validated concerns for high complication rates and reoperation rates of previous studies. The French TVM investigators now added to their recommendation for clinical trials to assess efficacy and complications a recommendation for studies to access the effects of PROLIFT on sexual function. In disregard for the concerning retrospective data of the TVM inventor and his colleagues as well as the growing pool of concerning prospective observational data from its own study, Ethicon neither pulled PROLIFT off the Market nor initiate the clinical trails recommended by its own experts.

(Iglesia, et al.):

[242] Conflicts of interest: Bernard Jacquetin holds the patent for Prolift, for which he receives royalties from Ethicon. B. Jacquetin, B. Fatton, C. Rosenthal, H. Clave, P. Debodinance, O. Garbin, J. Berrocal, R. Villet, D. Salet Lizee and M. Cosson all have had consultancy positions for Ethicon. P. Hinoul and J. Gauld are employed by Ethicon. This disclosure appears at the end of the article cited #217

In **August of 2010**, Iglesia et al published the early findings of their RCT on PROLIFT.[243] This study, randomized 65 women to PROLIFT (Total or Anterior) or traditional vaginal surgery.[244] This study, performed at Yale, Stanford, and Washington Hospitals, utilized 11 different validated questionnaires in the evaluation of subjective outcomes. The primary outcome was anatomic success, POP-Q of stage 0 or 1. The study protocol included predetermined safety criterion of 15% mesh exposure (extrusion). Enrollment in the study was halted when as the mesh exposure rate passed 15% (only 2/3rd of patients had reached the 3-month mark). At three months, no significant difference was noted in anatomic success or subjective symptoms. One hundred percent of he no-mesh group and symptoms and 93% of the mesh group reported cure of bulge symptoms. Eighty percent of mesh extrusions were surgically resected and 60% of mesh extrusions were resected in the operating room.

(Lucente letter to editor)

In **December of 2010**, Ethicon's paid consultant, Dr. Vince Lucente, wrote a letter to the editor regarding the Iglesia et al study.[245] Dr. Lucente suggested that the findings of Iglesia et al might be flawed secondary to performance bias. Dr. Lucente proposed that the study was flawed in that it did not control for the skill of the surgeon. Dr. Iglesia's response followed in that same publication, "Our trial was conducted by surgeons who were fellowship- trained, with expertise in all routes of reconstructive pelvic surgery, and who represent the skilled surgeons to whom new technology often is marketed. Furthermore, if a group of trained surgeons cannot achieve the results of a few mesh experts, then it is unlikely that general ob-gyns around the world, who do mesh repairs in even lower volumes, will achieve excellent results."[246] Ethicon however marketed PROLIFT to surgeons that were neither expert surgeons nor met their own internal definitions of the skilled surgeon appropriate for the PROLIFT procedure.[247] It is also important to note that performance bias is not unique to PROLIFT but exists for every medical device in the world. Performance bias is of greatest significance when a procedure requires great skill and extensive training to perform. Indeed, as noted elsewhere in this monograph, even the most experienced TVM surgeons in the world were unable to substantially improve their success or lower their complication rates.

(Neiminen, et al.):

---

[243] Iglesia CB, Sokol AI, Sokol ER, Kudish BI, Gutman RE, Peterson JL, Shott S. Vaginal mesh for prolapse: a randomized controlled trial. Obstet Gynecol 2010; 116: 293-303.

[244] Anterior Colporrhaphy, Posterior Colporrhaphy, Uterosacral Colpopexy or Sacrospinous colpopexy. Hysterecomy was optionally performed in both groups.

[245] Iglesia CB et al. Vaginal mesh for prolapse: a randomized controlled trial [Obstet Gynecol 2010; 116: 1456

[246] Iglesia CB et al. Vaginal mesh for prolapse: a randomized controlled trial [Obstet Gynecol 2010; 116: 1457.

[247] See Deopsition of Paul Parisi. Patricia Hammons v. Ethicon Womens Health and Urology.1/12/24. 766:15-767:23 and 769:14-24. See ETH.18412

In **September of 2010,** Neiminen and Hiltunen published a their final and 3-year follow-up of their 2007 study comparing anterior colporrhaphy to anterior colporrhaphy reinforced with Parietene. The extensive list of weaknesses of this study is covered in detail in my discussion of their 12 month (2007) and 24 month (2008) reports. This 3-year report focuses on the primary endpoint of anatomic recurrences and the secondary endpoints of symptom resolution, reoperation, and mesh exposure. At 3 years the mesh extrusion rate had increased remained at 19.5%. Although all extrusions were treated (40% resected in the O.R., 30% resected outside the O.R., and 30% treated with Estrogen) 25% of all extrusions persisted at 3 years.[248] Although the authors report 18% reoperation for POP in the no-mesh group and 11% in mesh group, they fail to comment on the overall reoperation rate and re-intervention rate. If we include the 8 women taken to the O.R. for mesh extrusion, the total reoperation rate in the mesh group is 18%. If we include the 6 women who were resected outside the O.R the overall surgical re-intervention rate is 24% for the mesh group vs. 18% for the no-mesh group. [249] Of even greater concern, the reoperation rate in the anterior compartment, the compartment of the primary end point of this study, was 6% for the mesh group and only 1% for the no-mesh group. The mesh group's questionably lower incidence in bulge symptoms reported at 2 years had disappeared by 3 years. The authors incorrectly report that after the first year "there seemed to be a similar gradual recurrence rate in both groups". The no-mesh group recurrence rate was 2.5% between 1 and 2 years and did not increase thereafter. The mesh group recurrence rate increased 4.3% between year 1 and 2 and than increased another 2% between years 2 and 3 (2.5 vs. 6.3 between years 1 and 3). With regard to the primary endpoint, the 3-year data demonstrated a significantly higher number of women in the no-mesh group with stage 2 or greater POP. However, there was no significant difference in symptoms between the groups.

The authors concluded, "We conclude that anterior colporrhaphy reinforced with mesh results in superior anatomic cure". This statement is not correct. As noted previously, the study only showed the anterior colporrhaphy reinforced with Parietene mesh, without fixation, not pulled through muscles, resulted in a significantly lower percentage of women with stage 2 or greater prolapse at 3 years, a finding that did not convey any symptomatic advantage. In exchange for this anatomic finding, women suffered a 19% incidence of the novel complication, mesh extrusion, a complication that required surgical intervention 70% of the time and was untreatable 25% of the time. In exchange for this anatomic finding that was not associated with any symptomatic advantage, women endured a higher surgical re-intervention rate. No meaningful conclusions can be made with regard to dyspareunia as the authors did not use a validated questionnaire and did not report on de novo dyspareunia. No meaningful conclusion with regard to dyspareunia can be made without this information. Finally, in order to compare PROLIFT to the method and findings of these

[248] The authors report that 70% of the 20 women with extrusions were resected. Of these 14 women, 8 were resected in the O.R.. Hence another 6 were resected outside the O.R.

[249] The authors report that 70% of the 20 women with extrusions were resected. Of these 14 women, 8 were resected in the O.R.. Hence another 6 were resected outside the O.R.

investigators, one would need to abandon the tools of PROLIFT, and not pull PROLIFT mesh through the obturator muscle. This would no longer be PROLIFT.

(Svabik, et al.):

In **September of 2010** Svabik et al manuscript, **Ultrasound appearances after mesh implantation evidence of mesh contraction or folding?** was published in the International Urogynecology Journal.[250] In this prospective observational study, PROLIFT anterior was measured with a ruler at time of implantation and then by ultrasound at 4 days and again at 3-5 months. Unlike the surgeons of the Tunn study and surgeons of the Shek and Dietz study who adjusted the mesh length to lay flat by trimming the mesh to 5 cm and 6.4-7.5 cm respectively (and sutured it to ensure in lay flat), Svabik et al purposefully used an oversized piece of mesh and placed it in a bunch and folded condition (FIGURE 6- Svabik at al Figure 1, mesh before closing incision). The average vaginal length prior to POP surgery is approximately 10.8 cm.[251] As PROLFIT and other kits for treating anterior POP are designed to cover (support) the proximal anterior compartment and spare the distal 3-4 cm (urethra and bladder neck), we expect intraoperative adjustments to result in lengths close to 6 cm (10.8 – 4 = 6.8). Whereas Tunn, Shek, and Dietz made such adjustment, Svabik at all did not. Svabik's implanted were adjusted to a mean of 9 cm. The only way 9 cm

[250] Svabík, Kamil, Alois Martan, Jaromir Masata, Rachid El-Haddad, Petr Hubka, and Marketa Pavlikova. "Ultrasound Appearances after Mesh Implantation—evidence of Mesh Contraction or Folding?" International Urogynecology Journal Int Urogynecol J 22.5 (2010): 529-33.

[251] Weber, Anne M., Mark D. Walters, and Marion R. Piedmonte. "Sexual Function and Vaginal Anatomy in Women before and after Surgery for Pelvic Organ Prolapse and Urinary Incontinence." .American Journal of Obstetrics and Gynecology</i> 182.6 (2000). 1611

can fit in a 6.8 cm space is to bunch or fold it, indeed this is what Svabik did (FIGURE 6).

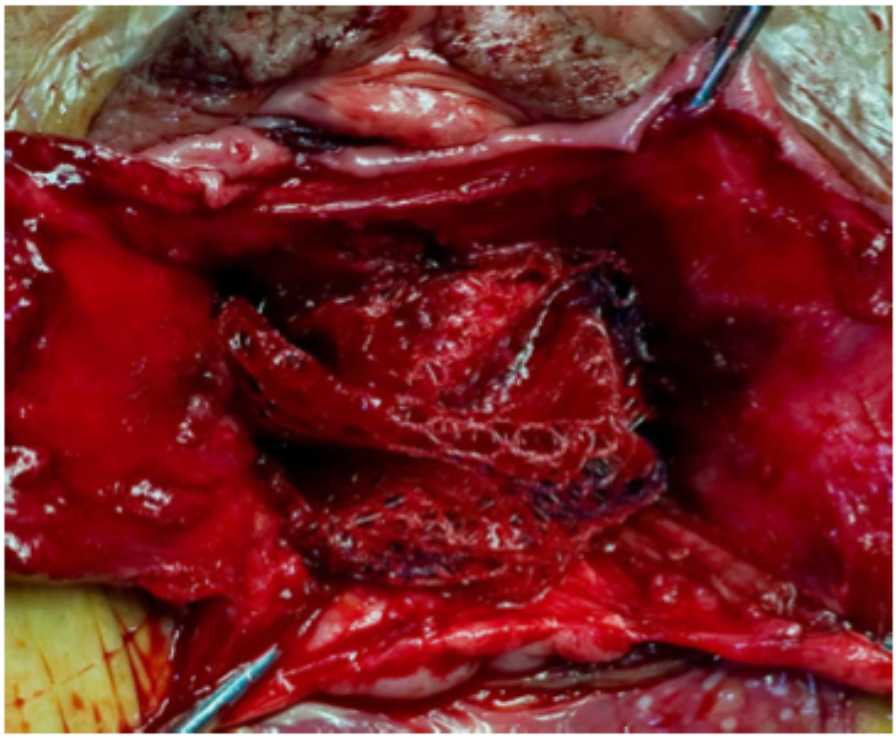


Fig. 1 Prolift anterior mesh folds—at site—before closing the vaginal skin and stretching of the mesh

FIGURE 6

The authors (Svabik, et al.) reported a 38% reduction in length (by ultrasound) at four days post implantation. Svabik suggests that such rapid reduction in size could not be secondary to shrinkage but could only be explained by surgical technique, folding. Svabik further indicates that this 38% loss of length, created by poor surgical technique, explains the majority loss of length previously described as contraction. However, anyone skilled in the art and perhaps anyone skilled in basic arithmetic can do the simple math; Other investigators adjusted their mesh intra-operatively to 5-7.5 cm in order to get it to lay flat. Svabik left 9 cm of mesh bunched up in that same space, a space that measures approximately 5-7.5 cm.

At the time of the 4-day post-implant ultrasound, the mesh was exactly as it was placed by Svabik, et al. (as is shown in FIGURE 6). Indeed, an ultrasound done in the recovery room would have found the mesh length to be in the 5-7.5 cm range. Furthermore, the folding and bunching of the mesh intentionally created by these investigators would cause substantial under-measurement of future contraction. As the mesh contracts, much of the shrinkage will be realized within the wadded and folded areas. Nonetheless, the investigators do note an additional 15% decrease in length at the second ultrasound (as high as 20% based on their reported

measurement error).[252] The ultrasound length of the PROLIFT at 3-5 months is only 53% of that measured at time of implant. The authors concluded "We observed a large and highly significant difference in pre- and postoperative dimensions of PROLIFT anterior mesh. Most of this difference seemed to be due to intraoperative folding rather than postoperative mesh retraction. This raises questions regarding the appropriate size of mesh implants and insertion technique".

The conclusion of the authors was correct. As described, Svabik, et al., deliberately placed implanted and oversized, bunched and folded PROLIFFT. This is evident from their intraoperative measurements (vs. known anatomy) and photo-evidenced as well. They are also correct that their study raised questions about the size of the mesh. The PROLIFT Anterior packaged length is approximately 11cm in length, the length of a normal vagina. Yet its method calls for limiting the implant to the proximal 2/3rd of the vagina and the labeling of the device discourages all but minor trimming.[253] Therefore, the size of the mesh and this teaching by Ethicon are in direct contradiction to the additional teaching of Ethicon, to lay the mesh flat. The authors were also correct to question the insertion technique. As discussed elsewhere in this monograph and also described by Ethicon, the blind passage of trocars created new complications not associated with traditional vaginal surgery. This study by Svabik brings to the front of the page the fact that neither leaving the mesh very loose nor trimming to a more anatomic size (Tunn, Shek, Dietz), prevents the final length from being only 20-50% of its implanted length. Furthermore, these investigators have also validated that which had already been demonstrated by Tunn, Shek, and Dietz, suturing the mesh in place does not prevent contraction. Finally, as explained, this study by Svabik et al demonstrates significant contraction of PROLIFT at 3-5 months. The second author, Alois Martan, was a paid consultant of American Medical Systems, the manufacturer of the Perigee device.

(Milani, et al.):

In **January of 2011**, a group of investigators including Ethicon's Director of Medical Affairs – World Wide (Piet Hinoul), Ethicon's Associate Director of Clinical Development (Judi M. Gauld), Ethicon's Associate Director-Health Economics & Reimbursement (Vanja Sikirica), and paid consultant Michel Cosson reported on Ethicon's one year RCT, Trocar-guided mesh repair of vaginal prolapse using partially

---

252 Svabík, Kamil, Alois Martan, Jaromir Masata, Rachid El-Haddad, Petr Hubka, and Marketa Pavlikova. "Ultrasound Appearances after Mesh Implantation—evidence of Mesh Contraction or Folding?" International Urogynecology Journal Int Urogynecol J 22.5 (2010): 531. Table 2

253 ETH.MESH.03960116 "If required, small reductions in the dimensions ofthe Total Implant to ensure proper fit should be performed at this point" .ETH.MESH.00658367-68. "While inexperienced surgeons initially may look for smaller pieces of mesh, the larger piece of mesh ¡s necessary to prevent bearing down on the vaginal capacity during healing". "This loose placement of mesh is often counterintuitive to the first time surgeon but is valuable in maintaining vaginal length".

absorbable mesh: 1 year outcomes.[254] The authors disclosed findings of previous studies on vaginal mesh, "The introduction of these new materials in pelvic reconstructive surgery has introduced new kinds of morbidity. Among the most prevalent complications are mesh exposure and shrinkage of tissue around the mesh. These may result in pelvic pain and dyspareunia. De novo dyspareunia after traditional POP repair ranges between 14.5% and 36.1% and a recent retrospective study reported a similar rate (16.7%) after repair with a mesh kit system. Indeed, a 2011 report by the lead author, Milani, found 26% de novo dyspareunia with PROLIFT. This study prospectively observed women with stage 3 or 4 POP following treatment with PROLIFT +M between April and October of 2008 (PROLIFT received FDA clearance for marketing on February 22, 2008). "The primary objective of this study was to assess anatomic and functional outcomes with this new mesh 1-year post-surgery. The secondary objective was to assess adverse events, particularly pain and dyspareunia". Anatomic success was defined as POP-Q of treated compartment less than stage 2. The Authors reported a failure rate of 22.6% (Upper Limit CI 31%). This was similar to that reported in Ethicon's French prospective observational TVM study (a rate that deemed the study a failure). The authors reported a 10.2% mesh exposure rate, a rate that was also similar to Ethicon's TVM studies. However, the de novo dyspareunia rate was remarkably lower than that of the prospective observational TVM studies and the RCT of the principle author, Milani. Whereas Milani had reported in a RCT of PROLIFT a 26% de novo dyspareunia rate, Milani herein reports a PROLIFT +M rate de novo dyspareunia rate of 2%. No significant change in TVL was noted. This is a remarkable finding as the authors explain that one of Ethicon's key rationales for bringing to market this modified PROLIFT, PROLIFT +M, was minimize tissue shrinkage which may lead to dyspareunia.

> "One of the key rationales for adopting a new, lighter-weight mesh with improved bidirectional elastic properties was to minimize tissue shrinkage, which may lead to dyspareunia. This new mesh is composed of a 50-50 blend of monofilament nonabsorbable polypropylene and absorbable polyglecaprone. Before absorption, this mesh weighs 57 g/m2. Full absorption after 90-120 days results in a final weight of 31 g/m2, as opposed to the 45 g/m2 of the original polypropylene mesh. Because of warp knitting, this mesh provides increased elasticity in the longitudinal direction and has larger pores compared with the original mesh to allow more tissue ingrowth".

Ethicon herein discloses that it has developed PROLIFT +M to solve the problem of PROLIFT contraction "which may lead to dyspareunia". Despite the concerns of investigator bias, this first prospective trial is exciting evidence suggesting that PROLIFT +M may indeed solve this PROLIFT problem without resultant loss of efficacy. However, Ethicon neither adds this learning to its labels nor initiates a RCT to compare the efficacy and complications of PROLIFT vs. PROLIFT +M. Whereas there existed a body of retrospective data (albeit concerning) on a prototype PROLIFT prior

[254] Milani AL, Hinoul P, Gauld JM, et al. Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1-year outcomes. Am J Obstet Gynecol 2011;204:74.e1-8. Ethicon positions verified on Linkedin.

to market introduction, clinical data on PROLIFT +M was remarkably absent. Yet In 2009 more than half of all PROLIFT devices sold would be PROLIFT+M.[255]

(Withagen, et al.):

In **February 2011,** a group of five surgeons, all paid consultants of Ethicon, published their one-year randomized controlled trial comparing PROLIFT to traditional native tissue surgery, Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse.[256] The primary endpoint was anatomic failure in any of the treated compartment by POP-Q stage 2 or greater. Women were randomized to either PROLIFT (anterior, posterior, or total) or conventional native tissue surgery (colporrhaphy with or without apical repair). Some PROLIFT patients also underwent a native tissue apical repair. A total of 194 women were randomized. The operating surgeon or a colleague performed postoperative POP-Q examinations. The authors found a significantly higher failure rate of the conventional surgery group (45.2 vs. 9.6%). However there was no difference in symptomatic or functional outcome (validated questionnaires were used). Although a statistical comparison of overall failures was performed, no comparison was made with regard to untreated compartment failure (these authors would report on this the following year). Mesh extrusion was noted in 16.9% of cases and only 22% treated with estrogen resolved. At one year, 50% of mesh extrusions persisted. The authors reported that approximately 3 patients needed to be treated with mesh to prevent one anatomic failure (greater than stage 1). Six patients needed to be treated with mesh to cause one harm. The authors reported that most anatomic failures were stage 2 and not bothersome enough to lead to surgery. Furthermore, the authors found no symptomatic benefit of PROLIFT (compared to native tissue surgery). Hence, every six PROLIFT surgeries would most likely harm one women and prevent two cases of minimally to asymptomatic stage 2 POP. Additionally, in the event that a surgeon would think that this was a reasonable trade-off, the surgeon would need to remember that this data only applies to women with recurrent POP. The authors stated, “Because the long-term effects and safety of mesh-reinforced repairs are not yet fully known, surgeons may consider these procedures primarily for recurrent vaginal prolapse after counseling patients on the risks and benefits”. In addition, the authors stated that, “The effects of long-term presence of nonabsorbable mesh in the vagina is unknown and a reason for concern”. Highlighting the growing concern that PROLIFT is a technically challenging surgery is the fact that mesh extrusion varied from 0-100% between centers. The findings as stated above, findings of Ethicon paid consultants, were never included in Ethicon’s physician or patient labels.

255

ETH.MESH.0772461I

256 Withagen, Mariëlla I., Alfredo L. Milani, Jan Den Boon, Harry A. Vervest, and Mark E. Vierhout. "Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse." Obstetrics & Gynecology. 117.2, Part 1 (2011): 242-50.

(Maher, et al.):

In **April of 2011**, Maher et al reported on their randomized control trial of Laparoscopic sacral colpopexy versus Total PROLIFT.[257] Fifty-five women were randomized to Sacrocolpopexy and 52 to PROLIFT. The primary outcome was anatomic success by POP-Q of less than stage 2 at two years. Secondary outcome included perioperative outcomes, patient satisfaction, quality of life outcomes, complications, and reoperations. Laparoscopic sacral colpopexy was significantly more successful than PROLIFT (77% vs. 43%, p<.001). Reoperation rate was significantly higher after PROLIFT (22% vs. 5%, =.006). PROLIFT was associated with significantly more blood loss, longer hospital stay, and a longer return to normal activities of daily living. Patient satisfaction by was significantly lower in the PROLIFT group. The total vaginal length (TVL) was significantly greater in the Sacrocolpopexy group (8.83 vs. 7.81 cm). In addition, the was no significant TVL change noted in the Sacrocolpopexy group (1mm, p<.001). The mean TVL change in the PROLIFT group was a loss of over 1.2 cm (p<.001). Mesh erosion was note in 13% of the PROLIFT group and 2% of the Sacrocolpopexy group (p=.07). This is yet another study demonstrating the high reoperation rate associated with PROLIFT.

(Dietz, et al.):

In **May of 2011,** Dietz and Shek published their second manuscript evaluating the post implantation shrinkage of an armed mesh with a TVM type method**.[258]** In this retrospective chart audit, women who had under implantation with Perigee (Armed Transobturator Anterior mesh kit, American Medical Systems) underwent two ultrasounds. The timing of the first ultrasound is not reported. However, it is stated that the first ultrasound was performed a minimum of 3 months post-implantation and the mean time to the second ultrasound was 18 months. Although there was no immediate post-implantation ultrasound, the authors disclosed that the mesh was trimmed to 5.0 x 3.7 cm. Based on this measurement and a second ultrasound mean length of 3.6 cm, mean shrinkage was 28%. Based on average post-native tissue surgery vaginal length between 8.4 and 9.8 cm, the mean post-contraction length of 3.6 cm reported herein would represent a maximum coverage of 42% of the vaginal wall.[259] Of great concern but not discussed by the authors is the fact that mesh elasticity (stretch) with valsalva was between 0 and 2%.[260] The importance of stretch is discussed elsewhere in this monograph and, as already noted, Ethicon taught that PROLIFT's "bi-directional elastic property allows adaptation to various stresses encountered in the body." Also documented in this manuscript is a 40% incidence of

---

[257] Maher CF, Feiner B, DeCuyper EM, et al. Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: a randomized trial. Am J Obstet Gynecol 2011 ;204:360.e1-7.

[258] Dietz HP, Erdmann M, Shek KL. Mesh contraction: myth or reality? Am J Obstet Gynecol 2011;204:173.e1-4.

[259] Tan, Jasmine S., Emily S. Lukacz, Shawn A. Menefee, Karl M. Luber, Michael E. Albo, and Charles W. Nager. "Determinants of Vaginal Length." American Journal of Obstetrics and Gynecology 195.6 (2006): 1846-850. Weber, Anne M., Mark D. Walters, and Marion R. Piedmonte. "Sexual Function and Vaginal Anatomy in Women before and after Surgery for Pelvic Organ Prolapse and Urinary Incontinence." .American Journal of Obstetrics and Gynecology</i> 182.6 (2000): 1611

[260] Dietz HP, Erdmann M, Shek KL. Mesh contraction: myth or reality? Am J Obstet Gynecol 2011;204:173.e1-4. Table 1

anatomic failure (stage 2 or greater) and a 27% overall incidence of recurrent symptoms. Although these investigators did not show significant shrinkage between the first ultrasound and the second ultrasound, there was already almost 30% shrinkage and complete loss of elasticity by the first ultrasound and 40% of patients had recurrent POP by the time of the second ultrasound. Dr. Dietz, the first author of this paper, discloses a financial relationship with the manufacturer of the Perigee implant (At the time of their 2008 publication which was more candid about mesh contraction, no such financial disclosure was made).Although Dr. Dietz concludes, "It maybe premature to enshrine the concept of mesh contraction in standardization documents dealing with mesh complications", this is a biased and nonsensical comment. Not only does this study validate the findings of Tunn et al and Velemir et al, it validates the original findings of Dr. Dietz and Shek, the transvaginal implantation of armed polypropylene mesh is associated with severe contraction and recurrent prolapse.

There are now no less than ten published studies that consistently demonstrated major concerns for lack efficacy and high complication rates, the majority of these studies authored by the developers of the TVM method. Ethicon continues to market PROLIFT, opts not to initiate any of the recommended studies or clinical trials, and fails to update its labels with the majority of the growing pool of concerning data. Surgeons throughout the U.S. and world continue to unknowingly implant the experimental and dangerous PROLIFT device into unknowing patients.

(Miller, et al. - Ethicon's U.S. 5-Year TVM data)

In **May of 2011,** a manuscript of the 5-Year Ethicon U.S. TVM data was published.[261] "The objective of the study was to assess the effectiveness and complication rates for the transvaginal (TVM) technique in the treatment of pelvic organ prolapse (POP)". As was true of the 6-month, 1 year, and unreported 3 year U.S. data, "The protocol defined success if the upper 90% 2-tailed CI did not exceed 20%, indicating we could be at least 95% certain the true failure rate was less than 20%". The authors reminded us "The primary effectiveness end point was prolapse recurrence, defined as an overall POP-Q stage II or more or surgical intervention to repair recurrence of vaginal prolapse". Although the authors did not disclose their financial relationships to the manufacturer, two of the three surgeons were paid consultants of Ethicon and the third author was Ethicon's World Wide Medical Director. This bias is evident in the reporting of the data. Rather than report the primary endpoint, recurrence of 33.3% (upper C.I. of 44.1%), the authors reported an anatomic success rate of 66.7% 9 (CI of 55.9-76.2). Not only does this distract the reader from the primary endpoint, it avoids the discussion of the fact that the study failed, by a large margin to meet its

[261] Miller, Dennis, Vincent Lucente, Elizabeth Babin, Patricia Beach, Peter Jones, and David Robinson. "Prospective Clinical Assessment of the Transvaginal Mesh Technique for Treatment of Pelvic Organ Prolapse-5-Year Results." Female Pelvic Medicine & Reconstructive Surgery 17.3 (2011): 139-43

success criteria, upper CI of 20%. According to the study protocol, the study was a failure.

Although only 66 patients were available for evaluation at 5 years, the authors chose to use the 85 (the original number of subjects) when calculating complications. This resulted in erroneous and misleading calculations. Mesh exposure was reported to be 19% (16/85) rather than the real number of 24% (16/66). Voiding dysfunction was reported to have occurred in 9% (8 /85) rather then the real number of 12%. Mesh exposure (extrusion) required surgical intervention in 50% of women. Of those women Fifty percent of all women who did not undergo surgical intervention for their mesh exposure had a persistent extrusion at five years. Rather than report the percentage of women with de novo urinary incontinence, the authors offered that 80% of women who did not undergo concomitant incontinence surgery remained dry. More smoke and mirrors. Although reoperations for complications and recurrent prolapse are discussed, the authors never offer the reader the total reoperation rate of 42% (1 rectovaginal fistula, on ureterovaginal fistula, 8 partial mesh excisions, 5 prolapse surgeries, and 13 incontinence surgeries). Discounting the overall reoperation rate of 42%, the authors offered that their 8% treated compartment re-operation rate was lower than that of traditional POP surgery citing a 13% incidence in a retrospective study from 1995. However, in keeping with the biased reporting of the data, the authors did not disclose that the 13% incidence reported in this traditional surgery study was an overall reoperation rate. The treated compartment re-operation rate was 1%.[262] Hence, the correct comparison of the U.S. TVM data to the cited traditional surgery data is : Overall reoperation rates of 42% vs. 13% (PROLIFT vs. Traditional Vaginal POP surgery) and treated compartment reoperation rates of 8% vs. 1% (PROLIFT vs. Traditional Vaginal POP surgery).

The authors report a 32% decrease in sexually active women following PROLIFT implantation. They also report an 11% incidence of de novo dyspareunia.[263] Bizarrely, even though their French counterparts had published similar findings (15% de novo dyspareunia and 35% decrease in sexually active women), the authors state "The results of this study, on the other hand, seem to confirm a net positive effect on sexual activity following prolapse surgery despite the use of mesh".

The authors conclude, "This is the first long-term study on the TVM technique, indicating that the technique offers durable anatomic support, although no unexpected late complications were observed. These long-term anatomic, functional, and safety data will be helpful when counseling patients regarding the outcomes of similar mesh procedures to treat POP." However Ethicon did not follow the advice of its World Wide Medical Director and paid experts. Ethicon would never add the

[262] Clark AL, Gregory T, Smith VJ, et al. Epidemiologic evaluation of reoperation for surgically treated pelvic organ prolapse and urinary incontinence. Am J Obstet Gyneco/2003;189:1261-1267. 1% calculation is based on vaginal POP surgeries..

[263] The authors report that all women with pre-existing dyspareunia had resolution, were no longer sexually active, or were lost to follow-up. Hence all dyspareunia at 5 years must be de novo.

outcomes such as study failure, 33% anatomic recurrence rate, 44% re-operation rate, 24% mesh extrusion rate, and 10% de novo dyspareunia to its labels.

In summary, although Ethicon's biased World Wide Medical Director and paid consultants provided a very misleading representation of the data, Ethicon's 5-year prospective observational data not only validated the worrisome findings of the previous five years, but presented even more concerning evidence that the risks outweighed the benefits. In an attempt to buffer the study's failure to demonstrate success, the authors offered an 89% anatomic success rate utilizing the more liberal definition of success, prolapse above the hymeneal ring. However, this success rate is not better than native tissue surgeries (using the same definition for anatomic success).[264] However, in exchange for, at best par anatomic success, this study and those before it show that women will be subject to a significantly increased number of re-operations, novel complications including mesh extrusion, decreased sexual activity, and high rates of dyspareunia and voiding dysfunction. In addition, failures and complications increased with time. Mesh remains in situ in perpetuity and complications and failures will continue to occur. In complete disregard for the growing pool of warnings provided by the numerous publications and the alarming findings at the conclusion of its five year prospective study (study failure and high complication rates), Ethicon neither pulled its product from the market nor initiated the any clinical trial to test the growing pool of convicting data. Of note, the publication of the Ethicon's 5-year U.S. TVM data was void of not only the financial disclosures of the author, but was also void of any reference to the fact that this was a study performed under its supervision and a manuscript it had a right to approve.[265]

(FDA Safety Communication to Health Care Providers)

In **July of 2011** the FDA issued a safety communication to health care providers and patients, UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse: FDA Safety Communication.[266] Included in its description of purpose, "The FDA is issuing this update to inform you that serious complications associated with surgical mesh for transvaginal repair of POP are **not rare**. This is a change from what the FDA previously reported on Oct. 20, 2008. Furthermore, it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair in all patients with POP and it may expose patients to greater risk". This updated followed the FDA's systematic review of the literature "showed that transvaginal POP repair with mesh does not improve symptomatic results or quality of life over traditional non-mesh repair." This Safety Communication from the FDA included:

---

[264] Chmielewski L, Walters MD, Weber AM, et al. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol 2011;205:69.e1-8.

[265] ETH.MESH.00401366,57,59,63,65,66

[266] http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm

- **Mesh used in transvaginal POP repair introduces risks not present in traditional non-mesh surgery for POP repair.**
- **Mesh placed abdominally for POP repair appears to result in lower rates of mesh complications compared to transvaginal POP surgery with mesh.**
- **There is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh.**
- **While transvaginal surgical repair to correct weakened tissue between the bladder and vagina (anterior repair) with mesh augmentation may provide an anatomic benefit compared to traditional POP repair without mesh, this anatomic benefit may not result in better symptomatic results".**

Additionally, the communication added,

- **"Mesh erosion can require multiple surgeries to repair and can be debilitating for some women. In some cases, even multiple surgeries will not resolve the complication."**
- **"Mesh contraction (shrinkage) is a previously unidentified risk of transvaginal POP repair with mesh that has been reported in the published scientific literature and in adverse event reports to the FDA since the Oct. 20, 2008 FDA Public Health Notification. Reports in the literature associate mesh contraction with vaginal shortening, vaginal tightening and vaginal pain".**
- **"Both mesh erosion and mesh contraction may lead to severe pelvic pain, painful sexual intercourse or an inability to engage in sexual intercourse. Also, men may experience irritation and pain to the penis during sexual intercourse when the mesh is exposed in mesh erosion".**

Expert Opinion on the 2011 FDA Safety Communication to Health Care Providers:

These bullet points communicated by the FDA are facts from its systematic review of the literature (level one evidence) and expanded on the previous systematic review finds of the Cochrane Group (2010). Although the FDA stated, "The complications associated with the use of surgical mesh for POP repair have not been linked to a single brand of mesh", the numerous prospective and retrospective studies completed by Ethicon and its group of paid expert consultants had consistently shown that its PROLIFT device was linked to these complications. A group of Ethicon's paid consultants and employees, including its World Wide Medical Director, had recently offered that it's PROLIFT device added additional new complications, "However, the introduction of vaginal graft augmentation with the use of trocars has introduced new complications that are not associated with traditional repairs, such as extra-pelvic

infections and mesh contraction, which cause pelvic and vaginal pain that often require further surgery".[267]

The FDA had limited ability to effectively distribute this information to its target audience, an audience that could include up to 50% of U.S. women and all gynecologists and urologists. Almost half of direct mail is never opened.[268] Email fairs even more poorly. "Open rates" for direct email communications ranges between 15-25%, with government communications reported to fall in the upper half of this range ">20%".[269] Most skilled in the art of communications recognize the efficacy of "point of purchase" marketing. By way of example, medical device sales representatives endeavor to meet with 100% of their surgeons and 100% of device boxes used in surgery get opened. Whereas the FDA had a very limited ability to effectively communicate to its target audience, the device manufacturers such as Ethicon had a highly effective means. Ethicon was already marketing directly to women considering POP surgery and implanters of mesh. Yet I can find no evidence that Ethicon included either this FDA communication or its breadth of valid facts in its labels (Instructions for Use, patient brochures, or advertisements). Ethicon knowingly opted not to inform its patients and surgeons of this concerning and valid data.

(Murphy, et al.):

In **July of 2011**, approximately one month after the release of the FDA Safety Communication, a group of six surgeons submitted for publication their response to the FDA communication entitled, Time to rethink: an evidence-based response from pelvic surgeons to the FDA Safety Communication: "UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse". [270]Five out of the six authors disclose one or more financial relationships to mesh manufacturers. This includes Dr. Vince Lucente who according to at least one report, has received about $800,000 from Ethicon (and additional monies from CR Bard and American Medical Systems).[271]

This group of industry-affiliated authors rebut some of the findings of the FDA's systematic review of the literature. Most of the rebuttals are peripheral and do not address the fact that the retrospective and prospective TVM (PROLIFT and Prototype PROLIFT) data is even more ominous that that reported in the systematic reviews.

---

267 Zyczynski HM, Carey MP, Smith ARB, et al. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:587.e1-8.

268 http://www.newsweek.com/junk-mail-keeps-post-office-alive-89323

269 https://www.mailjet.com/support/what-is-a-normal-open-rate,83.htm

270 Murphy, Miles, Adam Holzberg, Heather Van Raalte, Neeraj Kohli, Howard B. Goldman, and Vincent Lucente. "Time to Rethink: An Evidence-based Response from Pelvic Surgeons to the FDA Safety Communication: "UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse"." International Urogynecology Journal Int Urogynecol J 23.1 (2011): 5-9.

271 http://www.wsj.com/articles/SB10001424052702303546204579435162509926916

Indeed, in support of their rebuttals, the authors cite data which is predominantly non-TVM.[272] By way of example:

- These authors rebut the FDA's report of mesh contraction citing Dietz et al. They state this study showed no evidence of contraction between the first and second ultrasound. However, as discussed elsewhere in this monograph and not noticed by these authors, ultrasound demonstrated a mean decrease in size of 28%. The authors also opt not to cite the other published ultrasound studies, including a previous study by Dietz, that all show even greater amounts of contraction. The authors also offer seven RCTs to suggest that mesh does not result in a change in vaginal length. Three of these seven studies do not evaluate armed meshes. Of the remaining 4 cited studies, only two evaluated PROLIFT. One of these two studies, Altman et al, has fallen under great scrutiny by the New England Journal of Medicine secondary to industry involvement and does not report on TVL. The one study that reports on PROLIFT, Iglesia, a study in which enrollment was halted secondary to PROLIFT complications, did not find a difference in TVL change between native tissue surgery and PROLIFT. However, the study cited previously by these authors found that PROLIFT resulted in a significant decrease in TVL compared to Sacrocolpopexy.

These industry affiliated authors conclude, "However, there may be instances when a surgeon suspects that a native tissue repair will have a high risk of failure and that the potential benefits of a mesh repair outweigh the risks". Interestingly, they also include the following statement, "From our vantage point, it appears that the FDA has presented a biased view of TVM among all POP repair procedures because of the current reporting mechanisms in place". This is a curious statement as these authors are financially biased in the favor of mesh whereas the FDA is biased in favor of protecting patients.

(Withagen, et al.):

In **September of 2011,** Withagen, et al., reported on their prospective observational study, Risk Factors for Exposure, Pain, and Dyspareunia After Tension-Free Vaginal Mesh Procedure.[273] This data included 12-month follow-up of 294 women undergoing PROLIFT surgery (total, anterior, and or posterior). Excluding urinary tract infections, 18% of women suffered complications including one patient who suffered an injury to her obturator artery and received a blood transfusion equal to a 70kg person's entire blood volume. Mesh extrusion was reported in 12% of cases. De novo dyspareunia was noted in 26% of women. Risk factors for mesh exposure included smoking and Total PROLIFT (OR 3.1). Years of clinical and surgical experience (not the number of PROLIFT procedures) were found to be inversely associated with the risk of mesh

[272] Although TVM, tension free vaginal mesh, was an acronym initially reserved for the prototype PROLIFT and PROLIFT procedures, it eventually became used more broadly by some to mean "Transvaginal Mesh". In this report, TVM is used to describe the prototype PROLIFT procedure and PROLIFT.

[273] Withagen, Mariëlla I., Mark E. Vierhout, Jan C. Hendriks, Kirsten B. Kluivers, and Alfredo L. Milani. "Risk Factors for Exposure, Pain, and Dyspareunia After Tension-Free Vaginal Mesh Procedure.". Obstetrics & Gynecology. 118.3 (2011): 629-36.

exposure. The authors concluded "This study indicates that tension-free vaginal mesh surgery was safer if performed by more experienced urogynecologic surgeons". Three of the five authors, including the principle author, Dr. Withagen, were paid consultants of Ethicon.

(ACOG and AUGS Committee Opinion on Vaginal Mesh)

In **December of 2011**, The American College of Obstetrician and Gynecologists and American Urogynecology Society published its Committee Opinion, "Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse".[274] This opinion considered the pool of observational data, randomized controlled trials, and systematic reviews including Cochrane and the Society of Obstetricians and Gynecologists of Canada. The committee concurred with the findings of the FDA and previous systematic reviews and summarized their findings **"Based on available data, transvaginally placed mesh may improve the anatomic support of the anterior compartment compared with native tissue repairs; however, there are insufficient data on the use of mesh for the posterior or apical compartments. The risk/benefit ratio for mesh-augmented vaginal repairs must balance improved anatomic support of the anterior vaginal wall against the cost of the devices and increased complications such as mesh erosion, exposure, or extrusion; pelvic pain; groin pain; and dyspareunia**". **The committee recommended "Pelvic organ prolapse vaginal mesh repair should be reserved for high-risk individuals in whom the benefit of mesh placement may justify the risk, such as individuals with recurrent prolapse (particularly of the anterior compartment) or with medical comorbidities that preclude more invasive and lengthier open and endoscopic procedures".**

(de Landsheere, et al.):

In **January of 2012,** a large retrospective PROLIFT study was published in the American Journal of Obstetrics and Gynecology, Surgical intervention after transvaginal PROLIFT mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up.[275] This is a study that is commonly sited by Ethicon paid consultants in support of the PROLIFT device. When interpreting this report there are several very important factors that should never be overlooked.

- The study discloses that the majority of surgeries were done by Doctors Lucot and Cosson between 2005 and 2009. These are two of the most experienced TVM surgeons in the world.
- Women included in the study were examined two months after surgery and the only evidence of repeat examination is on those who required repeat

[274] Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse. Committee Opinion. Number 513. December 2011. Obstet Gynecol. 2011 Dec;118(6):1459-64. doi: 10.1097/AOG.0b013e31823ed1d9.

[275] de Landsheere L, Ismail S, Lucot J-P, et al. Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up. Am J Obstet Gynecol 2012;206:83.e1-7.

surgery. Hence, it is only evident that 61 of 524 patients (12%) were examined beyond two months. It appears as though the follow-up on the remaining women, 463 of 524 (88%) did not include a vaginal examination. These women were interviewed by phone.

- The follow-up is reported as a median and not mean of 38 months. Hence, it is possible that the mean follow-up phone call occurred much sooner than 38 months
- The study only reported on complications equal to or greater than Dindo grade 3. This means that erosions managed conservatively and infections opened at bedside or treated with I.V. antibiotics were not reported. Blood transfusion were not reported. Indeed the authors disclose "Reoperation rates only represent complications treated surgically and do not reflect the overall morbidity of the technique".
- 71% of the procedures performed by these expert TVM surgeons involved post anterior and posterior PROLIFT. This covers most or all of the vagina compartments with plastic (polypropylene). As demonstrated by the Ethicon's prospective French TVM data, this not surprisingly reduces or eliminates the known complication of untreated compartment failure. Therefore overall re-operation rates would be expected to be lower.

Taking these critical points into consideration, one may consider the reported data. Landsheere et al reported an 11.6% global re-operation rate. These same two expert surgeons, when they had 2-5 years of TVM experience rather than 3-9 years of TVM experience, reported an 18% global re-operation date. Although it is possible that years of experience have resulted in a re-operation rate of 11.6%, we must remember that, 11.6% is based on retrospective data and the majority of the follow-up was not done by telephone. Additionally, the authors excluded 7 patients who required re-operation (lost to follow-up). The inclusion of these patients would result in a 13% re-operation rate. Of final note, several of these investigators will later cite Diwadkar et al (a meta-analysis of re-operation rates and complication rates) which found traditional prolapse surgeries to be associated with a 5.8% reoperation rate (1.9% under general anesthesia). Hence, two of the most experienced TVM surgeons in the world are reporting a PROLIFT global re-operation rate 2-6 times greater than that reported by their subsequent citation, Diwadkar et al.[276]

Landsheere et al reported 3.6% mesh-related complications. This number only included patients undergoing mesh excision surgery. These two surgeons later publish a 50% rate of surgical intervention for mesh exposure.[277] Hence, it is likely that at least 7.2% of the patients examined in the two-month window suffered a mesh exposure. This number excludes complications managed conservatively (Dindo I or II). This number also excludes the 88% of women in this study who were interviewed only by phone other than those who reported surgery for their mesh complication. The phone query did not include questions about vaginal discharge, vaginal bleeding,

[276] Cited in the their 5-Year TVM manuscript.

[277] Cited in the their 5-Year TVM manuscript.

vaginal odor, male dyspareunia, patient palpation of mesh, office excision of mesh by another physician, or pelvic pain. Ultimately, the 3.6% mesh-related complications reported herein provide no meaningful information with regard to overall mesh-related complications.

Several of the huge weaknesses of this study, discussed above, are noted be the authors. They admit "Reoperation rates only represent complications treated surgically and do not reflect the overall morbidity of the technique". They authors add "Moreover, complications can be under estimated because some patients can present with an adverse event and choose not to undergo a surgery". This would include the 88% of women who were interviewed by phone and not queried about symptoms of mesh complications. Perhaps the most candid and insightful comment made by these authors was:

> "**A further potential bias of this report is that most of the procedures are conducted by surgeons with considerable experience in pelvic reconstructive surgery using mesh kits.** This element may explain the lower rates of complications when compared with other studies with smaller numbers. **Nonetheless, possessing such experience is essential before embarking on such techniques, and the findings of this study should underline this important message".**

This study provides only that the two of the most experienced surgeons in the world, surgeons with 3-9 years of TVM experience, could not demonstrate a significant decrease in the high overall reoperation rate associated with PROLIFT. Most concerning however is their caution to the world that "considerable experience" is essential before embarking upon PROLIFT (the TVM technique"

(Sokol, et al.):

In **January of 2012**, Sokol and Iglesia published the 1-year follow-up on the PROLIFT RCT, One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse .[278] At one year there remained no significant difference between either anatomic success or subjective improvement between the PROLIFT and native tissue repair groups. The authors reported a significantly higher rate or reoperation in the PROLIFT group, 15.6% vs. 0% in the mesh group. The PROLIFT re-operation rate also appears to have been under-reported. The authors disclosed 3 operations for excision of mesh and 3 operations for recurrent prolapse. This results in a 19% (6/32) re-operation rate.[279]

---

[278] Sokol AI, Iglesia CB, Kudish BI, et al. One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Am J Obstet Gynecol 2012;206:86.

[279] Although Table 5 lists only 2 reoperations for recurrent prolapse, the narrative on page E4 describes 3 reoperations for POP.

The authors concluded, "Lighter meshes and trocarless delivery systems likely will decrease complications that are associated with vaginal mesh use. Nonetheless, properly designed clinical trials are necessary to evaluate whether synthetic mesh confers benefit for vaginal prolapse repair. Based on the results of this study and the high exposure rates that have been noted in other studies, risks may outweigh benefits for the older trocar-based mesh systems, even when fellowship-trained pelvic reconstructive surgeons perform these procedures"

This January publication of the American Journal of Obstetrics and Gynecology includes two separate articles reporting on the PROLIFT re-operation rate. The prospective trial performed by fellowship trained surgeons demonstrated a 15.6-19% reoperation rate. The retrospective study, in which surgery was performed by two of the most experienced TVM surgeons in the world, demonstrated an 11.6% reoperation rate. Although Ethicon had believed for the past 7 years that PROLIFT was difficult to perform and a modification that abandoned the blind passage of arms through muscles could reduce complications, previous investigators had presented data in agreement with this concept, and a growing number of experts concurred, Ethicon neither updated its labels to reflect this information, limited is sales and marketing to expert surgeons, held the sales of PROLIFT, or performed the recommended clinical trials.

(Ethicon's PROLIFT+M Data Submitted for 522 Order)

On **February 1st of 2012** Ethicon revealed interim data from its ongoing RCT of PROLIFT +M vs. native tissue surgery.[280] Mean follow-up was under a year. Mesh extrusion, 14.8% was higher than reported in its observational study of 2012, but in line with the Ethicon's U.S. 1-year TVM data. De novo dyspareunia was 3.1%., This validated the findings of its 2009 prospective observational study and further substantiated the hypothesis that PROLIFT +M could lower dyspareunia rates. However, as noted above, mean follow-up was still less than one year. Curiously, no interim data is provided on the native tissue arm of the RCT. In summary, Ethicon introduced PROLIFT +M to solve PROLIFT associated complications. There is now growing level 2 evidence to suggest that PROLIFT +M can lower the rate of de-novo dyspareunia. Yet despite the fact that by 2011 PROLIFT +M accounted for 87% of overall PROLIFT sales, there were still no RCTs to support its safety and efficacy. The experiment continued.[281]

(The AUGS Transvaginal Mesh Tool Kit)

In **February of 2012** the American Urogynecology Society provided to its members its AUGS Transvaginal Mesh Informed Consent Toolkit. The initial publication of this

[280] Post Surveillance Study PS120043. Submitted to FDA in response to 522 order. Pg 14

[281] Post Surveillance Study PS120043. Submitted to FDA in response to 522 order. Pg 14

\

toolkit thanked four individuals for their work on the project. Two of these individuals had been paid consultant's of Ethicon.[282] The introduction of this toolkit to AUGS members stated, "Since the FDA's public health announcement on transvaginal mesh in July, one of our highest priorities has been to develop educational materials to help clinicians perform informed consent for patients who are considering mesh use for prolapse or incontinence". The Consent Toolkit provided numerous "risks and considerations". Among these risks and considerations highlighted by AUGS were several that had been specifically ignored or understated in PROLIFT labels:

- **Damage to the nervous system with pain or occasional motor dysfunction – incidence is rare (may be as high as 2%). When symptoms are associated with a focal area of mesh attachment and are disabling, stitch removal or removal of part of mesh is generally necessary. Removal or revision may not entirely resolve these problems.**
- **Adverse events requiring surgery are more common with mesh procedures than with non-mesh procedures; mesh exposure or erosion injuries caused by instruments used to insert the mesh are unique to these procedures. Other complications can also occur with non‒mesh procedures for POP.**

These risks and considerations, information AUGS believed was necessary for a patient to make an informed decision regarding PROLIFT, had never been part of the PROLIFT label or otherwise provided in any effective non-ambiguous, non-misleading way to potential patients.

(Withagen, et al.):

In **May of 2012**, Withagen et al, the group of Ethicon paid consultants who reported on their PROLIFT RCT in 2011, reported on their one-year prospective observation of 433 women with stage 3 and 4 POP or recurrent POP undergoing PROLIFT surgeries.[283] Concomitant native tissue surgeries were allowed. The authors reported a 15% failure rate in the PROLIFT treated compartment (stage 2 or greater) and an overall failure rate of 41%. The authors did not report on the untreated compartment failure rate. It is also important to remember that native tissue repairs in the untreated compartments may have reduced the untreated compartment failure rate and overall failure rate. Mesh exposure occurred in 13% of cases. The authors found that the use of the new partially absorbable PROLIFT was associated with an increased odds of failure (Defined as stage 2 or greater POP-Q). The use of isolated anterior or posterior PROLIFT, compared to Total PROLIFT was associated with significantly higher odds of failure. They also noted that the combined use of an anterior and posterior lift was associated with an increased risk of failure in all

[282] Peter Rosenblatt and Miles Murphy had previously disclosed financial relationships to Ethicon.

[283] Milani AL, Withagen MIJ, Vierhout ME. Outcomes and predictors of failure of trocar-guided vaginal mesh surgery for pelvic organ prolapse.
Am J Obstet Gynecol 2012;206:440.e1-8.

outcomes. Although the lowest risk of failure was associated with Total PROLIFT, these authors had previously demonstrated that Total PROLIFT was associated with a mesh exposure (extrusion) odds ration of 3.1. In summary, these paid Ethicon consultants demonstrated a 1-year overall anatomic failure rate of 41%. Although Total PROLIFT reduced this to 15%, this quite significantly increases the odds of the mesh extrusion. The authors did not attempt to correct for the concomitant use of native tissue surgery that may have artificially reduced the failure rate.

(Withagen, et al.):

In **October of 2012,** Withagen et al published a second analysis of their February 2011 RCT data that focused only on the treated compartment.[284] This study, Development of de novo prolapse in untreated vaginal compartments after prolapse repair with and without mesh: a secondary analysis of a randomised controlled trial, focused on the untreated compartment. Women treated in both compartments were excluded. When anatomic failure defined as Stage 2 POP-q or greater, 17% of women with native tissue repairs suffered an untreated compartment failure whereas 47% of PROLIFT patients suffered an untreated compartment failure (p<.001).[285] When anatomic failure defined as prolapse beyond the hymenal ring, 2% of women with native tissue repairs suffered an untreated compartment failure whereas 21% of PROLIFT patients suffered an untreated compartment failure (p<001).[286] Anterior PROLIFT resulted in 54% untreated compartment failure. However, when combined with native tissue apical repair, none failed (p=.002).
In summary, compared to native tissue repair, PROLIFT was associated with a ten fold higher rate of untreated compartment failure beyond the hymenal ring. This was associated with a significantly more bother. In addition, this study validated a growing concern amongst experts that the PROLIFT anterior device was defective at the apex.[287] This one year RCT, published as two distinct analyses by a group of Ethicon paid consultants, has failed to show any subjective benefit over traditional native tissue surgery, has demonstrated that PROLIFT results in 10 times the rate of untreated compartment failure, has demonstrated that such causes significantly more bother, and PROLIFT was associated with a 16.9% incidence of mesh vaginal mesh extrusion, few healing without surgical intervention.

(Ethicon's 5-Year French TVM data)

In **October of 2012**, nearly 1.5 years after the publication its U.S. 5-Year TVM data and nearly 2 year since the last study patient was completed, Ethicon's French

---

[284] Withagen M, Milani A, de Leeuw J, Vierhout M. Development of de novo prolapse in untreated vaginal compartments after prolapse repair with and without mesh: a secondary analysis of a randomised controlled trial. BJOG 2012;119:354–360.

[285] Table 3

[286] Table 3

[287] 2008 Daucher J, Alperin M. Modification of the anterior Prolift® mesh for reconstruction of anterior and apical vaginal prolapse. Tips and Tricks oral presentation at 2008 Annual Meeting of the American Urogynecologic Society. September 2008. and ETH.MESH .00003659, and Extraperitoneal Reconstruction with Modified Total ProliftTM to Optimize Vaginal Length with Coexisting Anterior and Apical Prolapse, Raders, J. SGS 2008

Investigators submitted their 5-year data for publication. In February of 2012, over two years since the final mesh implantation, Ethicon's 5-year French TVM data is published.[288] As per the study protocol, Ethicon had the right to review and approve this manuscript. The following disclosure is included with the published article:

> "Conflicts of interest Bernard Jacquetin holds the patent for PROLIFT® for which he receives royalties from Ethicon. B. Jacquetin, P. Debodinance, C. Rosenthal and M. Cosson have all held consultancy positions for Ethicon. B. Jacquetin, H. Clavé, M. Cosson and P. Debodinance have all accepted payment of travel expenses or honoraria from Ethicon. M. Cosson and P. Debodinance have all had acceptance of payment for research. P. Hinoul and J. Gauld are employed by Ethicon. **D. Salet-Lizée, R. Villet, J. Berrocal, B. Fatton and O. Garbin: no financial disclosures regarding Ethicon**".

Although the high degree of emotional and financial bias is remarkably evident, the authors (and Ethicon) mislead us to believe that 5 of the 12 authors are not financially biased. However, Ethicon and the authors are aware of the fact that this is a lie. Indeed, those same 5 authors disclosed financial interest in the publication of the 3-Year data from this same study:

> Conflicts of interest Bernard Jacquetin holds the patent for PROLIFT, for which he receives royalties from Ethicon. B. Jacquetin, **B. Fatton**, C. Rosenthal, H. Clave, P. Debodinance, **O. Garbin, J. Berrocal, R. Villet, D. Salet Lizee** and M. Cosson all have had consultancy positions for Ethicon. P. Hinoul and J. Gauld are employed by Ethicon.

The financial disclosure of the 2005 Ethicon Manuscript represents a blatant lie that misleads the reader to believe that almost half of the authors may have been void of financial bias. Even if the consultancy agreements of these five authors expired before the writing of the 5-year manuscript, all of the data prior to such would be subject to their financial bias and a conflict of interest for 3/5th of a study is still an obvious and known conflict of interest.

"The primary effectiveness end point was prolapse recurrence, defined as an overall POP-Q stage II or more or surgical intervention to repair recurrence of vaginal prolapse". At 5 years 21% (upper limit CI 30%[289]) met the definition of recurrence. "The upper limit of a 95% confidence interval (CI) for recurrence rate will be used to determine an outcome (success or a failure) for the study. If the upper limit of the CI for failure rate of prolapse surgery is below 0.20 (20%) then the study is a success,

---

[288] Jacquetin, B., P. Hinoul, J. Gauld, B. Fatton, C. Rosenthal, H. Clavé, O. Garbin, J. Berrocal, R. Villet, D. Salet-Lizée, P. Debodinance, and M. Cosson. "Total Transvaginal Mesh (TVM) Technique for Treatment of Pelvic Organ Prolapse: A 5-year Prospective Follow-up Study." .International Urogynecology Journal Int Urogynecol J</i> 24.10 (2013): 1679-686.

[289] Jacquetin, B., P. Hinoul, J. Gauld, B. Fatton, C. Rosenthal, H. Clavé, O. Garbin, J. Berrocal, R. Villet, D. Salet-Lizée, P. Debodinance, and M. Cosson. "Total Transvaginal Mesh (TVM) Technique for Treatment of Pelvic Organ Prolapse: A 5-year Prospective Follow-up Study." .International Urogynecology Journal Int Urogynecol J</i> 24.10 (2013):TABLE 2

otherwise it will be termed as a failure".[290] The upper limit documented by the French investigators of 30% is clearly in excess of the 20% failure criterion. The outcome of the study, as defined by Ethicon, is "failure". Of note, even the calculated failure rate (not the upper limit of CI), represents study "failure".

Distracting from the obvious failure of the study to meet its primary effectiveness endpoint, the authors indicated that a composite criterion of effectiveness (success), a composite success criterion, resulted in an 84% success rate.[291] The authors do not inform the reader that this criterion was not included in the study protocol. The authors also do not offer the reader that this composite PROLIFT success of 84% is less than composite success reported for native tissue POP surgery and not better than that reported for Sacrocolpopexy.[292]

Distracting from what is now an 18% re-operation rate[293], the authors offer only the calculated 5% rate of re-operation for recurrent POP (15% at 3 years). This 18% re-operation rate and the 42% re-operation rate reported in the Ethicon's U.S. study are both remarkably higher than the 5.8% traditional POP surgery re-operation rate (1.9% requiring anesthesia) reported in the study cited by the Ethicon's U.S. investigators.[294] The authors then attempt to compare their 5% POP re-operation rate to that of traditional surgeries claiming superiority. The authors cite studies by Clark et al and Benson et al. Clark et al is covered in my discussion of the Miller et al manuscript on Ethicon's 5-Year U.S. data. The treated compartment POP re-operation rate for the French TVM study (Total PROLIFT treats is designed to treat all compartments) is 5%. The treated compartment re-operation rate for Clark et al is 1% (not 13%as offered by the authors of the French TVM paper). The French authors also compare their 5% treated compartment re-operation rate to a "33%" rate reported by Benson et al for traditional vaginal surgery in 1996. However, the details of that study are conspicuously missing. A review of the Benson study demonstrates that the primary surgery performed for cystocele was a paravaginal repair, a repair that has been shown to be less effective than the much more commonly performed

---

290 ETH.MESH.00401351

291 The authors herein defined composite success as: "leading edge above the hymen (<0) and no bulge symptoms" The Ethicon study protocol defined reintervention as repeat surgery for prolapse and did not include pessary use for recurrent POP symptoms.

292 Chmielewski et al reported 89% composite success for anterior colporrhaphy. Chmielewski L, Walters MD, Weber AM, et al. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol 2011 ;205:69.e1-8. Barber et al reported an 85% composite success after Sacrocolpopexy.. Matthew D. Barber, MD, MHS, Linda Brubaker, MD, MS, Ingrid Nygaard, MD, Thomas L. Wheeler II, MD, MSPH, Joeseph Schaffer, MD, Zhen Chen, MS, and Cathie Spino, DSc. Defining Success After Surgery for Pelvic Organ Prolapse. Obstet Gynecol. 2009 September ; 114(3): 600–609. Both of these studies used a more stringent definition of composite success that excluded those who used a pessary to treat POP after implantation.

293 15 patients noted in 3-year manuscript. Now an additional patient has been operatied on twice for painful contraction and then for recurrent POP with a gracilis flap. This repeat surgery failed.

294 Diwadkar GB, Barber MD, Feiner B, Maher C, Jelovsek JE (2009) Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol 113 (2 Pt 1):367-373

anterior colporrhapy.[295] Of the 14 re-operations reported by Benson, 12 were in the anterior compartment. Excluding the anterior compartment that was that was treated with the uncommon and less effective method, the re-operation rate of Benson is 6%. Additionally, Benson et al does not make it clear that re-operations are occurring in the treated compartment. The 5% reoperation rate for treated compartments reported by the French authors is not lower than rates cited by these authors and distracts from the obvious, the overall reoperation rate is dramatically higher than that associated with tradition surgery.

The authors offer a single study by Altman et al to suggest superiority of PROLIFT in the anterior compartment. [296] They fail to disclose that this was an Ethicon sponsored study and Ethicon reviewed both the protocol and the manuscript prior to submission. The French authors point out that by using a composite outcome, PROLIFT Anterior was found to be more successful than native tissue anterior repair. However, the authors fail to include important material facts.
This same study demonstrated that PROLIFT was associated with significantly more blood loss, significantly longer operative times, significantly more de novo stress urinary incontinence (12.3 vs. 6.3%), and more than triple the rate of dyspareunia. Also, when evaluating for symptomatic cure (bulge symptoms), the post-operative rates were 75% vs. 62% (mesh vs. native tissue). In summary, this single study of PROLIFT anterior, sponsored by Ethicon, demonstrated a slightly higher rate of symptomatic improvement, significant increases in intra-operative issues and post-operative complications, and did not evaluate for the known and alarming issues identified by Ethicon's prospective observational studies: such as 50% reduction in sexual activity, 42% re-operation rate, 19% mesh extrusion rate, and vaginal contraction.

Mesh exposure (extrusion) has increased from 14.4% to 15.5%.
Although the number undergoing surgical resection and the number of persistent exposures at 5 years is documented, the concerning calculations are not offered to the reader. Fifty percent of patients with mesh exposure underwent surgical resection. At 5 years, 6 of the 7 women (86%) with mesh exposure whom were not treated with surgical resection had persistent mesh exposure.[297] Conservative management of mesh exposure has 86% of the time.

---

[295] Benson JT, Lucente V, McClellan E (1996) Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: a prospective randomized study with long-term outcome evaluation. Am J Obstet Gynecol 175:1418–1422. Chmielewski L, Walters MD, Weber AM, et al. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol 2011;205:69.e1-8. Abramov Y et al. Site-specific rectocele repair compared with standard posterior colporrhaphy. Obstet Gynecol 2005; 105: 314-318.

[296] Altman D, Väyrynen T, Engh ME, Axelsen S, Falconer C, Nordic Transvaginal Mesh Group (2011) Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse. N Engl J Med 364(19):1826–1836

[297] 7 women had persistent mesh exposure. 1 of the 7 women had failed a previous surgical resection. Hence, only one of the 7 persistent extrusions could represent a previous resection. We know that 7 women were resected and one failed. Therefore, only one of the persistent exposures is a previously resected patient. By default, 6 of the 7 women with persistent extrusion have not undergone resection. If 14 women suffered exposure and 7 were surgically corrected, 7 women were not surgically corrected. There are 6 women whom were not treated with resection in the persisent extrusion group. Therefore 6/7, 85% or those not resected persited.

Although the authors report a slight decrease in the de novo dyspareunia rate to 10%, there has also been a dramatic decrease in the number of sexually active women (35% drop in sexually activity at 3 years, 46% at 5 years). The authors do not report if any of the patients with de novo dyspareunia at 5 years had de novo dypspareunia at 3 years. Seven women who were sexually active at 3 years are no longer sexually active at 5 years. It is possible that the six women with dyspareunia at 3 years are amongst the seven who are no longer sexually active. Hence, the dyspareunia rate at 5 years may be as high as 27%.[298] However, of even greater concern is the fact that there has been an almost 50% decrease in sexually active women since PROLIFT implantation. The authors offer only "In our study, we failed to capture reasons for discontinuation of sexual activity." Even though mesh complications continue for the life of the implant, the authors concluded "Finally, we suggest that sexuality should not be studied for longer than 3 years in studies addressing POP surgery as it no longer reflects the impact of that surgery".

This 5-Year prospective evaluation of PROLIFT failed to meet its success criterion. By its own definition of failure, it was a failure. At five years the upper limit confidence interval for failure was 30%. Comparisons of PROLIFT to native tissue surgery failed to demonstrate a benefit. This report of Ethicon's 5-year French prospective TVM study provide offer no findings that contradict the concerning finding already demonstrated by their 1 and 3 year data, by the U.S. 1,3, and 5 year data, or the growing pool of literature. Rather, the findings of this report validate the growing pool of alarming findings. The French and U.S. data show that PROLIFT is associated with an outstandingly high need for re-operation (18-42%), an outstandingly high rate of de-novo dyspareunia (10-27%), a mesh extrusion rate of 17-24%, a 32-46% reduction in sexual activity, and was also associated with at least a 12.6% of vaginal contraction. These concerning findings were reported by a group that was biased toward favorable reporting.

(Cochrane, Maher, et al.):

In **April of 2013**, the Cochrane Group updated its systematic review of the literature, Surgical management of pelvic organ prolapse in women.[299] This review found 56 trial including 5954 women**. The authors concluded, "In general, there is a lack of evidence to support transvaginal mesh operations used in apical or posterior compartment surgery".** With regard to the anterior compartment they did report a reduced risk of recurrent treated compartment failure and symptoms. They however cautioned, that this must be weighed against disadvantages including longer operating time, greater blood loss, prolapse in other areas of the vagina, new onset urinary stress incontinence, and the mesh becoming exposed in the vagina in 11% of

[298] Please see my discussion of the 3-year data abstract and full manuscript that demonstrates six women with de-novo dyspareunia. Those 6 women plus the three described with de novo dyspareunia at 5 years results in up to 9 (of 33 sexually active women) with de novo dyspareunia).

[299] Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD004014. DOI: 10.1002/14651858.CD004014.pub5.

women. This systematic review of the literature by the Cochrane group, representing the highest level of evidence, validates what Ethicon's TVM group had reported in multiple retrospective and prospective studies since 2005. Of note, the majority of PROLIFT studies discussed in this monograph demonstrated higher mesh exposure rates and dyspareunia rates than the pooled dated of this systematic review.

(da Silviera, et al.):

In **September of 2014**, da Silviera et al reported on their Brazilian RCT, Multicenter, randomized trial comparing native vaginal tissue repair and synthetic mesh repair for genital prolapse surgical treatment.[300] This one-year trial randomized women with stages 3 or 4 POP to either site-specific native tissue repair performed with 0-Polypropylene suture combined with sacrospinous colpopexy or PROLIFT. Although no difference was found between the anatomic cures in the apex and posterior compartments, the authors found a significantly higher anterior compartment anatomic cure rate in women undergoing anterior mesh repairs. Both groups demonstrated significant QoL improvements. Although the authors reported a significantly greater QoL improvement in the PROLIFT groups, the authors did not stratify this by treated compartment. Hence, we do not know if there exists a significant QoL advantage of mesh or native tissue repair in particular compartment. It is possible that there was a significantly higher native tissue QoL improvement. Although this study demonstrates an anatomic and possibly a QoL benefit in the anterior compartment, the results are not generalizable to the majority of patients considering POP surgery. Firstly, this study limited treatment to only patients with more advanced grades of POP. Indeed, many if not the majority of patients treated by general gynecologist have lesser stages of POP. Secondly, the native tissue arm of this RCT was restricted to site-specific repairs with 0-polypropylene suture, rather than the more common and more efficacious midline colporrhapy with delayed absorbable suture.[301] Furthermore, the use of this less efficacious native tissue surgery could be the sole cause of the anatomic and QoL differences reported favorably for the PROLIFT arm.

In summary, this RCT demonstrated that PROLIFT provided a superior anterior compartment anatomic outcome and possible superior QoL compared to a type of site-specific native tissue surgery uncommonly performed in the U.S. combined with sacrospinous colpopexy in a group or women with stage 3-4 POP. However, in exchange for the noted anatomic benefit in this subset of women with advanced POP, the women suffered a 20-23% mesh erosion rate and more than double the

---

[300] Simone Dos Reis Brandão Da Silveira, Jorge Milhem Haddad, Zsuzsanna Ilona Katalin De Jármy-Di Bella, Fernanda Nastri, Miriam Goncalves Markos Kawabata, Silvia Da Silva Carramão, Claudinei Alves Rodrigues, Edmund Chada Baracat, and Antonio Pedro Flores Auge. "Multicenter, Randomized Trial Comparing Native Vaginal Tissue Repair and Synthetic Mesh Repair for Genital Prolapse Surgical Treatment." .International Urogynecology Journal Int Urogynecol J</i> 26.3 (2014): 335-42.

[301] Chmielewski L, Walters MD, Weber AM, et al. Reanalysis of a randomized trial of 3 techniques of anterior colporrhaphy using clinically relevant definitions of success. Am J Obstet Gynecol 2011;205:69.e1-8. Abramov Y et al. Site-specific rectocele repair compared with standard posterior colporrhaphy. Obstet Gynecol 2005; 105: 314-318.

reoperation rate. [302] In order to provide valuable data to U.S. surgeons, this study would need to be repeated with the more commonly performed and more efficacious native tissue colporrhaphy. If such a study demonstrated similar results, and those results were subsequently validated, a surgeon could inform a patient with symptomatic stage 3 or 4 anterior POP, that although native tissue surgery and PROLIFT both tend to improve anatomic findings and QoL, PROLIFT may provide a greater improvement, but is associated with a 20-23% rate of mesh exposure and more than double the re-operation rate. That surgeon should of course provide that same patients with the additional data on PROLIFT including an up to 47% untreated compartment failure rate, a de novo dyspareunia rate of up to 26%, and the risk of mesh related contraction and exposure symptoms, and the unique difficulties associated with the treatment of such symptoms.

SUMMARY OF CLINICAL DATA AND RELATED COMMUNICATIONS

PROLIFT appeared on the U.S. market in **2005** in the complete absence of any level on evidence of safety of efficacy. Indeed, the world new nothing about the safety and efficacy of this novel method that involved the blind passage of trocars through nerve and vessel rich spaces and muscles. In 2005 the entire pool of published evidence consisted of concerning data published by the biased inventor and developers of the prototype PROLIFT device and procedure. This 2005 data included a 12% incidence of mesh erosion (75% undergoing surgical intervention) and what was described as a worrying rate of recurrent prolapse at only 3 months. Sales continued. In **2006** completed the analysis of its French 1-Year observational TVM data. This study, by Ethicon's predetermined definition, was a failure. The failure rate was 18.8% with the upper confidence interval reaching 26.6% failure. At least one of the eight centers had a 100% failure rate. Reoperation occurred in 18% of patients. Moderate to severe contraction was noted in 12.6% of patients. Ethicon would not release this report for publication. Also in 2006, retrospective data from French TVM investigators would demonstrate an approximately 40% reoperation rate at less than four months. Ethicon did not update its labels to reflect this information. Sales continued.

Between **2007 and 2008** published data became even more concerning. An ultrasound study on PROLIFT demonstrated 61-65% contraction following implantation. An ultrasound study on a different armed mesh device, Perigee yielded similar findings. Some of the 3-year findings of Ethicon's French TVM study were reported in an abstract. A 35% reduction in sexual activity was demonstrated. Additionally, 71% of non-excised mesh extrusions persisted. Also published was a RCT and a prospective observational study involving modifications of the PROLIFT that abandoned the blind passage of arms with trocars. These studies both demonstrated mesh erosion rates lower than those being reported for PROLIFT without a suggestion of lower efficacy. Interesting is the fact that Ethicon internal

[302] The erosion rate is 23% if the one rectal erosion is included.

documents reveal it believed, since 2004, that it could reduce the complications of its procedure by altering the TVM method and ceasing to pass mesh arms through muscles of the pelvis.[303] Several authors indicated the need for randomized controlled trials to demonstrate safety and efficacy. Ethicon did not update its labels to reflect these findings. Ethicon did not initiate randomized controlled trials. Furthermore, the FDA issued a Public Heath Notice to healthcare providers regarding transvaginal mesh. In the is notice, the FDA warned that rare complications associated with mesh could have serious consequences. Ethicon new the listed complications were not rare with PROLIFT. It did not update its labels to reflect this. Sales continued.

Between **2009 and 2010** another RCT utilizing the no-trocar, no-blind-pass modification of PROLIFT demonstrated a mesh extrusion rate that was lower than that of PROLIFT. A group of investigators including Ethicon the inventor of PROLIFT and investigators from Ethicon's French TVM study reported on their assessment of mesh contraction utilizing both physical examination and ultrasound. These authors found evidence of moderate to sever contraction in 89% of women and noted that over 2/3rd of women with anatomic failure had severe contraction (less than 6% of non-failures had severe contraction). These authors reported "In conclusion, our study suggests that recurrence after TVM repair of anterior and posterior vaginal wall prolapse is associated with severe mesh retraction and loss of mesh support on the lower part of the vaginal walls". These were some of the most experienced TVM surgeons in the world. Several years since the abstract, the full manuscript of Ethicon's 3-year French TVM data was published. The recurrence rate had increased to 20% (upper limit CI of 28.5%) and the de novo dyspareunia rate was 12.8-15.3%. This data was validated by the prospective evaluation of 323 women by Fatton, Jacquetin, and Lagrange who reported evaluated native tissue surgery vs. PROLIFT. These authors, the most experienced TVM surgeons in the world, found PROLIFT to be associated with significantly more de novo dyspareunia (15.4% vs. 2%). [304] This same year, Iglesia et al pre-maturely halted enrollment in their PROLIFT RCT when the erosion rate exceeded the predetermined safety cut off of 15%. Lastly, a group reporting on their 3-year follow-up of an armed mesh documented an increase in mesh extrusion to 19.5%. Even though 100% of patients were treated for mesh extrusion, 30% persisted. Reoperation rate was 18% and re-intervention in the anterior compartment was 6 times higher in the mesh group than the native tissue group. The material facts of this growing and concerning pool of data remained absent from the PROLIFT labels. Sales continued.

In **2011** a group of Ethicon's paid consultants reported, in their RCT, a 16.9% mesh extrusion rate and 50% of these extrusions persisted at one year. Also in 2011 Maher et al reported on their RCT of Laparoscopic Sacrocolpopexy (LSC) vs. Total PROLIFT. These authors found a significantly higher success rate associated with LSC (77% vs. 43%) and a significantly higher reoperation rate with PROLIFT (22% vs. 5%). These

---

303 ETH.MESH.07902335. PROJECT INITIATION PROPOSAL

304 Fatton B, Lagrange E, Jacquetin B. SEXUAL OUTCOME AFTER TRANSVAGINAL Repair Of Pelvic Organ Prolapse (Pop) With And Without Mesh: A Prospective Study Of 323 Patients. ICS/IUGA S7. August 25. 2010.

authors also found PROLIFT to be associated with a significantly shorter postoperative vaginal length, significantly more blood loss, significantly longer hospital stay, and a significantly longer time to return to activities of daily living. LSC was also associated with a significantly higher level of patient satisfaction. This same year saw the publication of Ethicon's U.S. 5-year prospective TVM data. This data demonstrated a 33% failure rate (upper CI of 44.1%), a 24% incidence of mesh extrusion (50% having undergone surgery for such), a 10% de novo dyspareunia rate, a 32% reduction in sexual activity, a 13% incidence of re-operation in the treated compartment (vs. 1% in the native tissue study cited by the authors), and a 42% overall re-operation rate. Withagen's report of a PROLIFT RCT revealed a 26% incidence of de novo dyspareunia. These authors also found a significant inverse relationship between years of clinical and surgical experience and mesh extrusion. They concluded "This study indicates that tension-free vaginal mesh surgery was safer if performed by more experienced urogynecological surgeons." Additionally this year, Milani with a group including several Ethicon employees reported on Ethicon's prospective observational study of its new PROLIFT +M, a modified PROLIFT that it hoped would decrease contraction and dyspareunia. Indeed, this study demonstrated a de novo dyspareunia rate of 2%, substantially lower than that known to PROLIFT. Following a review of the available literature, the American College of Obstetricians and Gynecologists and the American Urogynecology Society published its Committee Opinion which concluded "The committee recommended "Pelvic organ prolapse vaginal mesh repair should be reserved for high-risk individuals in whom the benefit of mesh placement may justify the risk, such as individuals with recurrent prolapse (particularly of the anterior compartment) or with medical comorbidities that preclude more invasive and lengthier open and endoscopic procedures". None of these statistics and important communications would be included in the PROLIFT labels. Sales continued.

In **2012** Sokol, et al., reported one-year follow-u on their RCT. Significantly more re-operations were noted in the PROLIFT group compared to the native tissue group (15-19% vs. 0%). Withagen's group reported again on their RCT. They noted an overall 47% non-treated compartment failure and 54% non-treated compartment failure associated with PROLIFT anterior. PROLIFT was found to be with a 10 times greater incidence of non-treated compartment failure. Also this year, Ethicon reported its 5-year prospective French TVM data. This study, also deemed a failure by Ethicon, found a 21% failure rate (upper limit CI of 30%), and 18% re-operation rate, an increase in mesh extrusion to 15.5% (86% not treated with resection persisted), and a further fall in sexual inactivity from 35 to 46%. The most experienced PROLIFT surgeons in the world achieved these concerning results. This same year, the American Urogynecology Society published for its members a mesh consent toolkit for patients. Included in its narrative were warnings of pain and motor dysfunction that might not entirely resolve with removal or revision of mesh and a statement that adverse events are more common with mesh surgeries, and injuries caused by instruments used to insert mesh are unique to these procedures.

These concerning material facts and communications never appeared in PROLIFT labels.

On **February 1st of 2012** Ethicon submitted its plan to the FDA.[305] This plan did not contain any RCT data collection for PROLIFT and offered early interim data (mean less than one year follow-up) on its PROLIFT + M RCT by Dr. Withagen. This data however did provide additional validation for the hypothesis that PROLIFT +M could reduce the de novo dyspareunia rate of PROLIFT. Conspicuously missing was the native tissue arm. **April 2nd of 2012** Ethicon was notified by the FDA of numerous deficiencies in its plan. On **May 9th of 2012** Ethicon notified the FDA that, in light of the complexities of the clinical study requirements, adverse publicity, and litigation environment, it would be discontinuing the commercialization of its PROLIFT device.[306]

In **2013** the Cochrane group updated its already concerning systematic review on the Surgical management of pelvic organ prolapse in women The authors concluded, "In general, there is a lack of evidence to support transvaginal mesh operations used in apical or posterior compartment surgery". With regard to the anterior compartment they did report a reduced risk of recurrent treated compartment failure and symptoms. They however cautioned, that this must be weighed against disadvantages including longer operating time, greater blood loss, prolapse in other areas of the vagina, new onset urinary stress incontinence, and the mesh becoming exposed in the vagina in 11% of women.

On January 4th of 2016 the FDA reported that it had reclassified transvaginal prolapse mesh from a moderate-risk device to a high-risk device. Coincident to this, it issued the requisite order "that requires all manufacturers to submit a premarket approval application (PMA) to support the safety and effectiveness of surgical mesh for the transvaginal repair of POP. This is the same PMA that Ethicon avoided in 2005 and again in 2007.

Expert Opinion of Clinical Data and Ethicon's Response to the Clinical Data:

As a user of medical devices, as a preceptor who has trained over one thousand surgeons on the use of medical devices, as CEO and COO of medical device companies, as a labeling consultant to medical device companies, as a consultant to companies marketing medical devices, and based on my knowledge, training, experience and review of the medical literature as well as my review of testimonies and discovered documents, I state with a reasonable degree of medical and corporate certainty that Ethicon had knowing marketed an experimental device and method (PROLIFT) since 2005, knowingly ignored a growing pool of data that demonstrated high and concerning complications, knowingly ignored data that failed to demonstrate an

[305] ETH.MESH.07724600

[306] ETH.MESH.04005092

efficacy equal to or superior to traditional vaginal surgery, knowingly ignored the recommendations of its own experts to perform prospective clinical trials (and RCTs), withheld and or obscured concerning findings of it one observational prospective trial, knowingly failed to update its labels with critical material facts regarding it product, failed to initiate any clinical trial on its PROLIFT and PROLIFT + M devices, and relied on data from a financially and emotionally biased investigators that was predominantly based on a prototype surgery that has substantial difference from the already marketed PROLIFT; This behavior by Ethicon is a deviation from that expected by surgeons using a medical device, a deviation from principles of medical ethics, and a deviation from industry standards; This behavior of Ethicon resulted in continued and increased use of the PROLIFT device resulting in substantial injury to women of the world.

DEVICE DEFECTS. METHOD DEFECTS. ALTERNATIVES

EXPERT OPINION: THE MATERIAL WAS DEFECTIVE.

The Human Body Has and Adverse Effect on Polypropylene.
The PROLIFT implant is a cut piece of GYNEMESH PS. GYNEMESH PS is made of polypropylene mesh. The PROLIFT +M implant is cut from a piece of ULTRAPRO. ULTRAPRO is, in its majority, is made of Polypropylene mesh. Although it is beyond the scope of this report to teach the microbiology of the human immune system or material science, the basic components of such provide a simple explanation of how and why polypropylene mesh (PPM) implantation is associated with acute and chronic inflammation, oxidation, degradation, scaring, contraction, and loss of elasticity. This is not scientific or medical theory. These are hard medical and scientific facts that have been demonstrated, consistently, in both retrospective and prospective studies.

PPM is a foreign body. It is a attacked by the innate immune system. The attacking cells act to breakdown and digest the foreign body in a process call phagocytosis. When a non-biodegradable foreign body is implanted permanently and is too large to be phagocytized, a process of frustrated phagocytosis occurs. In frustrated phagocytosis, macrophages and foreign body giant cells (hereby referenced as "FBGCs") release mediators of degradation into zone between the cell membrane and the implanted material surface. PMNs and Macrophages (and FBGCs) , immune cells responsible for this attack, release increasing amounts of the powerful oxidizing agents: ionized oxygen, hydrogen peroxide, and hypochlorite. Reactive oxygen intermediates can cause surface oxidation with degradation polypropylene.

One of the worlds larger manufacturers of the polypropylene resin used to fabricate PPM materials acknowledged and warned that "the material like other polyolefins (the type of plastic used to make polypropylene), can be attacked by some strong mineral acids, halogens, and oxygen. The effect of strong oxidizing agents is an attack

on the polymer chain resulting in eventual embrittlement of the resin," and that these molecules can attack the polyproylene resin "causing degradation of the resin."[307] Among these chemicals that are known to "attack" this polypropylene and cause the embrittlement and degradation are (1) oxygen, and (2) hydrogen peroxide, and (3) Hypochlorite. The exact chemicals released in the above described reaction of the human body to the implanted PPM. A classical study, known in the art since 1976, demonstrated that the remarkable oxidative changes of implanted PPM. Even though the oxygen concentration in human tissue is substantially less than room air, this study demonstrated that the oxidative changes occurring to implanted PPM were greater than would be expected with exposure to 100% oxygen.[308] This extreme oxidation can only be explained by the well-demonstrated inflammatory response (and associated release of hydrogen peroxide, hypochlorite and reactive oxygen species by inflammatory cells). Numerous studies have since confirmed the oxidative degradation of implanted PPM with resultant contraction and loss of elasticity.[309] A recent study published in the Journal of Material Science not only further validated the in vivo degradation of PPM, but found that such degradation was not evident in other meshes; "The polypropylene mesh demonstrated chemical degradation via oxidation, permanent distortion of the mesh, and changes in thermal properties. While chemical degradation was not conclusively evident in PET and ePTFE....,."[310] even studies offered by the few remaining advocates of transvaginal PPM implantation demonstrate significant contraction of the PPM with almost complete loss of elasticity.[311] Although the loss of elasticity and contraction is in part secondary to the severe scaring created by the foreign body reaction, studies that have removed the scar have demonstrated that the mesh remains contracted and inelastic.[312]

As noted above, the body's attach on PPM with subsequent degradation is a fact supported by decades of evidence. An article from 1982 similarly discussed that polypropylene can degrade from the formation of free radicals inside the body, and explained that "[t]he effects of these degradation processes will naturally vary, but generally there will be a change in average molecular weight, molecular-weight distribution, crystallinity and mechanical properties." A 1994 article describes the

---

307 TSM 308: Chemical Resistance of Marlex Polyproylene. Phillips Sumika

308 Liebert, Timothy C., Richard P. Chartoff, Stanley L. Cosgrove, and Robert S. Mccuskey. "Subcutaneous Implants of Polypropylene Filaments." .Journal of Biomedical Materials Research J. Biomed. Mater. Res.</i> 10.6 (1976): 939-51.

309 Fayolle B, Audouin L, Verdu J. Oxidation induced embrittlement in polypropylene - a tensile testing study. Polymer Degradation and Stability. 2000;70(2000):333-40. Wood, A. J., M. J. Cozad, D. A. Grant, A. M. Ostdiek, S. L. Bachman, and S. A. Grant. "Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient." .J Mater Sci: Mater Med Journal of Materials Science: Materials in Medicine</i> 24.4 (2013): 1113-122. Dietz HP, Erdmann M, Shek KL. Mesh contraction: myth or reality? Am J Obstet Gynecol 2011;204:173.e1-4. Dietz HP, Erdmann M, Shek KL. Mesh contraction: myth or reality? Am J Obstet Gynecol 2011;204:173.e1-4. Tunn, R., A. Picot, J. Marschke, and A. Gauruder-Burmester. "Sonomorphological Evaluation of Polypropylene Mesh Implants after Vaginal Mesh Repair in Women with Cystocele or Rectocele." .Ultrasound in Obstetrics and Gynecology Ultrasound Obstet Gynecol</i> 29.4 (2007)

310 Wood, A. J., M. J. Cozad, D. A. Grant, A. M. Ostdiek, S. L. Bachman, and S. A. Grant. "Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient." .J Mater Sci: Mater Med Journal of Materials Science: Materials in Medicine</i> 24.4 (2013): 1113-122.

311 Costello, C. R., S. L. Bachman, B. J. Ramshaw, and S. A. Grant. "Materials Characterization of Explanted Polypropylene Hernia Meshes." Journal of Biomedical Materials Research Part B: Applied Biomaterials J. Biomed. Mater. Res83B.1 (2007): 44-49.

312 Costello, C. R., S. L. Bachman, B. J. Ramshaw, and S. A. Grant. "Materials Characterization of Explanted Polypropylene Hernia Meshes." Journal of Biomedical Materials Research Part B: Applied Biomaterials J. Biomed. Mater. Res83B.1 (2007): 44-49.

adverse biological effects of oxidative degradation of implant polymers, stating that the oxidative process "will augment any tissue injury due to the invading organisms. These highly reactive radicals generated by cellular mechanisms at or near the surface of implanted polymers may contribute to damage of the polymer surface in the same fashion as established polymer degradation reactions by reactive radicals." The authors in the article entitled Biodeterioration/Biodegradation of Polymeric Medical Devices In Situ explained the cycle of foreign body response to a polymer implant material and degradation.[313] The authors explained that the "vicious cycle" results in "poor compatibility" and "can result in serious tissue response, where different enzymes and active species released from cells can damage the implant profoundly, the degradation products then possibly making the tissue response even worse."[314] Additionally, "mechanical stress may affect degradation"[315] as a result of loading under service. Wood et all summarized in their 2013 evaluation of mesh explants, "Unfortunately, polypropylene will degrade in an oxidizing environment, such as the environment during a foreign body response."[316]

The foreign body reaction is also associated with the release of chemical messengers know as cytokines. These cytokines are responsible for recruiting more inflammatory cells. Cytokines are also well known to be associated with sympathetic nerve sprouting and chronic pain. Recent evaluation of vaginal mesh explants and abdominal mesh explants has demonstrated that vaginal mesh explants have 11 times the number of entrapped nerve fibers.[317] The continued degradation of the polypropylene mesh creates more rough surface area, more acute and chronic inflammation, recruiting even more macrophages and FBGCs, which cause more degradation, thus creating a problematic environment.[318] This is a viscous cycle of inflammation. The persistence of the foreign body reaction for the lifetime of the device indicates that the oxidation process is continuous. Klinge et al have demonstrated that implanted mesh continues to behave as a chronic wound eight years after implant.

Polypropylene Has an Adverse Effect on the Human Body. As described earlier in this report, the innate immune system recognizing and attacks foreign material. This is known as the foreign body reaction (FBR). Different materials are associated with different degrees of FBR. In the best-case scenario, the material is associated with only a minimal FBR and a mild, short-lived FBR occurs. In the worst-case scenario, a protracted severe FBR occurs. We are all familiar with the signs of a FBR, redness,

---

313 Zhong, S.P. et al. *Biodeterioration/Biodegradation of Polymeric Medical Devices In Situ,* International Biodeterioration & Biodegradation, Vol. 130, 95 (1994).

314 Id.

315 Id, at p. 108.

316 Wood, A. J., M. J. Cozad, D. A. Grant, A. M. Ostdiek, S. L. Bachman, and S. A. Grant. "Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient." .J Mater Sci: Mater Med Journal of Materials Science: Materials in Medicine</i> 24.4 (2013): 1113-122.

317 In The United States District Court For The Southern District Of West Virginia Charleston Division In Re: Boston Scientific Corp. Pelvic Repair System Products Liability Litigation MDL No. 2326 Iakovlev General Expert Report

318 See e.g. Anderson et al, *Foreign Body Reaction to Biomaterials,* Seminars in Immunology 20 (2008) 86-100.

warmth, swelling, pain, and loss of function. Indeed, medical students are given these words to memorize in Latin: rubor, calor, tumor, dolor, functio laesa.

In their paper arguing for decreasing the amount of polypropylene implanted (deceasing the total amount of polypropylene used in a piece of mesh), Cobb et al state "The long-term consequences of implantable polypropylene prosthetics are not without concern. The body generates an intense inflammatory response to the prosthetic that results in scar plate formation, increased stiffness of the abdominal wall, and shrinkage of the biomaterial". This problem is well known in both the medical and scientific art. Multiple investigators have demonstrated the dramatic difference between a repair performed with native tissue and suture compared to one performed with polypropylene mesh. The authors demonstrated that, unlike the native tissue repair, the polypropylene (ppm) repair did not heal and continues to behave like both an acute and chronic wound.[319] Although decreasing the inoculum (the amount of polypropylene) may decrease the severity of the FBR, the problem of the severe FBR with ongoing acute and chronic inflammation persists and may even worsen.[320] Acute and chronic inflammation are associated with both pain and loss of function.[321] Indeed the most common complication reported in the FDA's systematic review of transvaginal mesh are those associated with inflammation: extrusion and pain.

From the foregoing as well as my knowledge, training, and experience, it is my opinion to a reasonable degree of medical certainty that vaginal implantation of the PROLIFT and PROLIFT+M, composed of polypropylene, results in acute and chronic inflammation, degradation, contraction, and loss of elasticity when implanted in the human vagina; This is material science that is not known to those the typical user (surgeon) of PROLIFT and or PROLIFT+M; The vaginal implantation of polypropylene, a material that degrades, contracts, and becomes inelastic is unreasonably dangerous for implantation in the human vagina; The polypropylene material of PROLIFT and PROLIFT+M is defective; Additionally, this information regarding the defective nature of polypropylene is abundant and known to Ethicon, which took measures to

---

[319] U. Klinge, B. Klosterhalfen, V. Birkenhauer, K. Junge, J. Conze, and V. Schumpelick. Impact of Polymer Pore Size on the Interface Scar Formation in a Rat Model. JOURNAL OF SURGICAL RESEARCH: VOL. 103, NO. 2, APRIL 2002. Klosterhalfen, B., Klinge, U., Hermanns, B., and Schumpelick, V. [Pathology of traditional surgical nets for hernia repair after long-term implantation in humans]. Chirurg 71(1): 43, 2000.

[320] Arnaud Clavé & Hannah Yahi & Jean-Claude Hammou & Suzelei Montanari & Pierre Gounon & Henri Clavé. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J (2010) 21:261–270. Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591. U. Klinge, B. Klosterhalfen, V. Birkenhauer, K. Junge, J. Conze, and V. Schumpelick. Impact of Polymer Pore Size on the Interface Scar Formation in a Rat Model. JOURNAL OF SURGICAL RESEARCH: VOL. 103, NO. 2, APRIL 2002. Klosterhalfen, B., Klinge, U., Hermanns, B., and Schumpelick, V. [Pathology of traditional surgical nets for hernia repair after long-term implantation in humans]. Chirurg 71(1): 43, 2000.

[321] Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591

decrease the amount of polypropylene in its device. [322]

EXPERT OPINION: THE MESH WAS DEFECTIVE

The pore size was defective. Decades in advance of the marketing of PPM mesh for transvaginal implantation; the abdominal hernia literature demonstrated a high incidence of severe inflammation, scarring, contraction and pain. Polypropylene mesh implantation in the treatment of abdominal hernias began decades prior to its use in vaginal surgery. Indeed, the original PPM implants used for vaginal surgery had obtained their 510K marketing approvals as abdominal hernia mesh implants or claimed such as predicates. Although PPM had been shown to decrease the recurrence rate of abdominal hernias, the loss of abdominal wall compliance and pain became a substantial problem. Prolonged patient discomfort and chronic pain were know to occur as often 20% and 50% of the time, respectively.[323] Looking at normal abdominal wall compliance, Junge et all reported that hernia meshes should have at least 25% vertical stretching and 15% horizontal stretching.[324] Ethicon indicated in 2006 "Elasticity in the range of 20–35% has been reported to match the compliance of surrounding tissues to avoid both extrusion of the material and patient discomfort".[325] Anyone skilled in the art should recognize that the vagina, an organ requisite to sexual intercourse and pelvic organ support, would need, at a minimum, an implant with similar compliance.

Well in advance of the of the May 2008 PROLIFT and PROLIFT +M clearance for marketing, in 2007, Muhl et al reported on effective porosity. Muhl demonstrated that, in order to allow tissue ingrowth and prevent the bridging fibrosis and its resultant mesh contraction, poor sizes needed to remain greater than 1000 microns under the typical loads seen following implantation.[326] Muhl defined the pores remaining after such in vivo loading as "effective porosity". It is well known that PPM textiles, at time of implantation, are compliant. The surgical implantation immediately stretches the mesh as does the load created by in vivo pressure / activity. This stretch as been shown to change the pore shape and size. The result is always, a smaller effective pore.

---

[322] Ethicon continued to decrease the amount of polypropylene in its products. It migrated from PROLINE mesh to GYMNEMESH PS and eventually to ULTRAPRO. Reasoning is also described in a publication of its paid consultants and employees. Milani AL, Hinoul P, Gauld JM, et al. Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1-year outcomes. Am J Obstet Gynecol 2011;204:74.e1-8.

[323] ÕDwyer PJ, Kingsnorth AN, Molloy RG, et al. Randomized clinical trial assessing impact of a lightweight or heavy- weight mesh o n chronic pain after inguinal hernia repair. Br J Surg 2005;92:166–170.Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591

[324] K. Junge á U. Klinge á A. Prescher á P. Giboni M. Niewiera á V. Schumpelick. Elasticity of the anterior abdominal wall and impact for reparation of incisional hernias using mesh implants. Hernia (2001) 5: 113±118

[325] Barbolt, Thomas A. "Biology of Polypropylene/polyglactin 910 Grafts." International Urogynecology Journal Int Urogynecol J.17.S1 (2006): 26-30.

[326] Muhl, et al. New Objective Measurement to Characterize the Porosity of Textile Implants. J. Biomed Mater Res Part B: Appl Biomater 84B:176-183, Publishe on line May 2007.2008. Klinge U, Klosterhalfen B. Modified classification of surgical meshes for hernia repair based on the analyses of 1,000 explanted meshes. Hernia DOI 10.1007/s10029-012-0913-6.

Yet, Ethicon chose not to measure its native poor size or effective poor size. Ethicon acknowledged that poor size had not been measured during product development, "Pore size in microns was not measured during the development of the PROLENE Soft Mesh (aka GYNEMESH PS). The total percent area that is open was measured and is considered an accurate method. Since the product construction results in irregular pore geometries and size, it is not accurate to report a distinct pore size."[327] Not only has Ethicon known since 2006 that many GYNEMESH PS pore are smaller than 75 microns (too small to allow a penetration by a single macrophage) and had knows since at least 2007 that its GYNEMESH PS was subject to bridging fibrosis, recent evaluation has demonstrated an complete loss of porosity under load (no effective pores).[328] Although Ethicon later offered ULTRAPRO mesh (PROLIFT +M) as a mesh with larger pore size that could decrease bridging fibrosis, shrinkage and dyspareunia, it did not validate the effective pore size of ULTRAPRO nor discontinue the marketing and sales of GYNEMESH PS (PROLIFT).[329]

From the foregoing as well as my knowledge, training, and experience, it is my opinion to a reasonable degree of medical certainty that PROLIFT'S GYNEMESH PS fostered bridging fibrosis, the pore size of GYNEMEHS PS was significantly too small to prevent bridging fibrosis with resultant unreasonably dangerous contraction[330], this is information that would not be anticipated by either the surgeon or the patient, and this is information that with was known by Ethicon; The pore size of the PROLIFT mesh was defective.

EXPERT OPINION: THE MESH IMPLANT OF THE PROLIFT AND PROLIFT +M DEVICES WAS DEFFECTIVE.

The Importance of Normal Vaginal Anatomy. There is perhaps no organ in the human body more important than the vagina. Obstetricians often jest that the heart's

---

[327] ETH.MESH.01431617, 6-14/15-2006, email chain about Gynemesh PS/Prolene Soft mesh pore size, Robert Rousseau: (Ethicon principal engineer)

[328] ETH-83788: 1-26-2006. Otto J, Kaldenhoff E, Kirschner- Hermanns R, Muhl T, Klinge U. Elongation of textile pelvic floor implants under load is related to complete loss of effective porosity, thereby favoring incorporation in scar plates. J Biomed Mater Res A 2014;102:1079-84. Barone W, Moalli P, Abramowitch S. Vari- able porosity of common prolapse meshes during uni-axial loading. Female Pelvic Med Reconstr Surg 2013;19(Suppl 2):S56. ETH.MESH.01818397. An Investigational Study of Swine Models to Evaluate Mesh Contraction and Tissue Integration Over a 13 Week Period

[329] Milani AL, Hinoul P, Gauld JM, et al. Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1-year outcomes. Am J Obstet Gynecol 2011;204:74.e1-8.

[330] Please see the numerous citations of the scientific literature found in 5. THE CLINICAL DATA and ASSOCIATED COMMUNICATIONS of this report describing thedangerous amount of contraction including but not limited to studies by authors such as Velemir, Dietz, Sheck, Tunn. Feiner, Benjamin, and Christopher Maher. "Vaginal Mesh Contraction." .Obstetrics & Gynecology.115.2, Part 1 (2010): 325-30. as well as Arnaud Clavé & Hannah Yahi & Jean-Claude Hammou & Suzelei Montanari & Pierre Gounon & Henri Clavé. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J (2010) 21:261–270. Dirk Weyhe, MD, Inge Schmitz, PhD, Orlin Belyaev, MD, Robert Grabs, Klaus-Michael Mu¨ller, MD, Waldemar Uhl, MD, Volker Zumtobel, MD. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does Not Mean Less Biological Response. World J Surg (2006) 30: 1586–1591. U. Klinge, B. Klosterhalfen, V. Birkenhauer, K. Junge, J. Conze, and V. Schumpelick. Impact of Polymer Pore Size on the Interface Scar Formation in a Rat Model. JOURNAL OF SURGICAL RESEARCH: VOL. 103, NO. 2, APRIL 2002. Klosterhalfen, B., Klinge, U., Hermanns, B., and Schumpelick, V. [Pathology of traditional surgical nets for hernia repair after long-term implantation in humans]. Chirurg 71(1): 43, 2000.. see also ETH.MESH.01818397. An Investigational Study of Swine Models to Evaluate Mesh Contraction and Tissue Integration Over a 13 Week Period

purpose is to pump blood to the vagina and the brain's purpose is to keep it safe. Human existence is predicated on propagation and the propagation of the human species is uniquely dependent on the female urogenital organ, the vagina. Yes it is true that other species propagate in a similar fashion to humans. Yet human propagation is much more complex. The perpetuation of the human genome is in no small way predicated on the success of family unit. The human male-female bond created by the intimacy of sexual experience is part of the glue of marital relationships and long-term partnerships and satisfaction with sexual relationships has been shown to be significantly associated with better, more stable, happier marriages. The loss of this intimacy can undermine this relationship and disrupt the entire family unit.[331] Numerous researches have demonstrated the association between sexual dysfunction, marital problems and divorce.[332]

A normal vagina is not only vital to human relationships and the family unit; it is necessary to maintain normal bowel and bladder function. The connective tissues and muscles supporting and surrounding the vagina coincidentally support the bladder and rectum. Any adverse change in the material properties of these supporting structures can cause a woman to suffer from debilitating urinary incontinence, fecal incontinence, severe constipation, and or urinary retention. However, more devastating are the effects on coital function, as the injury extends beyond the patient harming the entire family unit.

Contraction of the mesh was of unpredictable severity and caused significant harm. As described above in the section titled **The pore size was defective**, it is important that a material being implanted in the treatment of a hernia provides the necessary elasticity (compliance) to treat the hernia without causing pain or impairing function. As pointed out by Ethicon, the abdominal hernia literature indicates that hernia graft material should stretch 20-35%. Although the literature is less replete with estimations of requisite vaginal graft compliance and I can find no evidence that Ethicon endeavored to find this information, the consequences of underestimating this requirement are clearly grave. As the normal vagina, in a resting state substantially smaller than and elongated and flattened lemon can expand to accommodate a baby, it is clear that the natural elasticity of the connective tissue surrounding the vagina is greater than 20-35%. Any mesh implant that provides less elasticity will, at a minimum, be creating a less compliant vagina. As covered in detail

---

[331] See Atwood, J. D., & Dershowithz, S. (1992). Constructing a sex and marital therapy frame: Ways to help couples deconstruct sexual problems. Journal of Sex and Marital Therapy, 18, 196–219; Spence, S.H. (1997). Sex and relationships. In W. K. Halford & H. J. Markman (Eds.), Clinical handbook of marriage and couples interventions (pp. 73–105). New York: John Wiley.

[332] See for example, Bakhshayesh, A., &Mortazavi, M. (2009). Relationship Satisfaction, Sexual Health and Marital Satisfaction in Couples. Applied Psychology, 3: 4 (12): 85-73; Ali-akbari Dehkordi, M. (2010). Relation between Women's Sexual Function and Marital Adjustment. Journal of Behavioral Sciences , 4:13, 199-206; Lau, T.F. J., Yang, X., Wang, Q., Cheng, Y., Tsui, Yi. Hi., Mui, W.H. L., & Kim, H. J. (2006). Gender Power and Marital Relationship As Predictors of Sexual Dysfunction and Sexual Satisfaction among Young Married Couples in Rural China: A Population-Based Study, Urology, 67(3):579-585; Chen Yeh, H., Lorenz, O. F., Wickrama, K.A.S. Conger, D. R., & Elder Jr. H. G. (2006). Relationships among Sexual Satisfactin, Marital Quality, and Marital Instability at Midlife, Journal of Family Psychology , 20(2):339-343; Trudel, G., & Goldfarb, M. R. (2010). Marital and sexual functioning and Dysfunctioning, Depression and Anxiety, Sexologies, 19(3):137-142. See also, Ata Shakerian, Ali-Mohammad Nazari, Mohsen Masoomi (2014). Inspecting the Relationship between Sexual Satisfaction and Marital Problems of Divorce-asking Women in Sanandaj City Family Court. Procedia - Social and Behavioral Sciences 114 (2014) 327 - 333.

in THE CLINICAL DATA and ASSOCIATED COMMUNICATIONS section of this report, the severe and unpredictable contraction of implanted polypropylene mesh is an established problematic fact. PROLIFT contraction has been shown to occur in 89% of women, average 61% at 6 weeks, continue for years, vary in degree, result in loss of most or all elasticity, and according to the inventor and developers of PROLIFT and other key opinion leaders to be responsible for pain, erosion, and failure of the device.[333]

This is consistent with my clinical experience. I have explanted hundreds of pieces of polypropylene mesh including PROLIFT and PROLIFT +M from the vagina of women suffering from mesh extrusion, dyspareunia, pain, and bowel and bladder dysfunction. All of these explants demonstrated complete loss of flexibility and elasticity and where extremely hard and or brittle. All of these surgeries demonstrated severe contraction of the mesh. Those explanation surgeries associated with successful explanation of large portions of the mesh have often resulted in moderated improvement in symptoms. Unfortunately, such broad explantation is often not possible.[334]

One size does not fit all. The inventor of the PROLIFT procedure recommended three to accommodate variances in patient anatomy. Six Expert surgeons recruited by Ethicon for collection of its GYNEMESH PS Device Validation data cut six different size pieces for repair a cystocele (Range: 4 x 2.5 to 11 x 8cm).[335] Clearly, one size does not fit all women. Yet Ethicon not only created a single sized device but cautioned surgeons against anything but minor alterations in size.

Contraction and loss of elasticity of the PROLIFT and PROLIFT +M results in significant and often severe morbidity. As described in THE CLINICAL DATA and ASSOCIATED COMMUNICATIONS section of this report and acknowledged by Ethicon therein, this phenomenon results in a high rate of de novo dyspareunia, vaginal shortening, and recurrent pelvic organ prolapse. As a result of such, PROLIFT and PROLIFT +M are associated with a re-operation rate that is significantly higher than that of traditional native tissue surgery.

Although de novo dyspareunia and vaginal shorting are certainly complications that also occur in native tissue surgeries, the dyspareunia and vaginal shortening associated with PROLIFT is much more problematic. Most dyspareunia that occurs following native tissue surgery is transient and or responds to conservative

---

[333] See Tunn, Shek, Dietz, Velemir, the retrospective studies of the French TVM investigators all covered at length in the Clinical Data section of this reports and Letouzey V, Deffieux X, Levailolant J, et al. Ultrasound evaluation of polypropylene mesh contraction at long term after vaginal surgery for cystocele repair (abstract). Int Urogynecol J Pelvic Floor Dysfunct. 2009;20:S205 and Feiner, Benjamin, and Christopher Maher. "Vaginal Mesh Contraction." .Obstetrics & Gynecology.115.2, Part 1 (2010): 325-30.

[334] Approximately 50% of cases by my clinical experience and that of other. Crosby, Erin C., Melinda Abernethy, Mitchell B. Berger, John O. Delancey, Dee E. Fenner, and Daniel M. Morgan. "Symptom Resolution After Operative Management of Complications From Transvaginal Mesh." .Obstetrics & Gynecology. 123.1 (2014): 134-39.

[335] ETH.02089268

management such as physiotherpy. Vaginal shortening associated with native tissue surgery responds well to the use of vaginal dilators. However dyspareunia associated with mesh contraction and vaginal shortening is most typically non –responsive to non-surgical intervention. The explanation is simple. The natural vaginal wall is elastic, it stretches. Contracted, degraded mesh is inelastic. The post implant plastic cannot be stretched by physiotherapy or dilators. Yet, if a surgeon can resect the majority of the vaginal mesh of PROLIFT and cut the PROLIFT arms at their attachment points, stretching of the vagina occurs and as many as 50% or more of patients experience improvement. This is consistent with my clinical experience that includes over a thousand native tissue surgeries, over a thousand mesh surgeries, and the treatment of hundreds of complications of the armed meshes (including many PROLIFT's). These findings are also consistent with the published reports of other experts.[336]

From the foregoing as well as my knowledge, training, and experience, it is my opinion to a reasonable degree of medical certainty that the mesh implants included with the PROLIFT and PROLIFT +M device consistently contracted to an unpredictable size, lost nearly all elasticity, were provided in a single size even though no two female pelvises are the same size, and that these troublesome characteristics of the mesh made the results and complications of the POP surgery unpredictable, caused substantial increases in POP surgical morbidity and reoperation, harming both women and their families; This is information that would not be anticipated by either the surgeon or the patient, and this is information that with was known by Ethicon; The mesh of the PROLIFT and PROLIFT +M devices was defective

EXPERT OPINION: THE GYNEMESH OF PROLIFT WAS DEFECTIVE IN COMPARISON TO OTHER COMMERCIALLY AVAILBLE MESHES

In **2003** Ethicon completed its 91 day rat study comparing its GYNEMESH PS (PROLENE SOFT) to other polypropylene mesh products.[337] This study utilized a non-validated method of quantifying tissue reaction that was implemented by its employed PhD. This study noted that inflammation in all meshes persisted at 91 days. The study also demonstrated that GYNEMESH PS was uniquely prone to erosion down to muscle with adherence to muscle. This unique and concerning characteristic was noted in 60% of the GYNEMESH PS rats and 0% of the six other meshes tested (including Ethicon's PROLENE and "Bard Mesh"). Also of great concern, GYNEMESH PS was associated with a reduction of connective tissue, whereas Ethicon's PROLENE

[336] Crosby, Erin C., Melinda Abernethy, Mitchell B. Berger, John O. Delancey, Dee E. Fenner, and Daniel M. Morgan. "Symptom Resolution After Operative Management of Complications From Transvaginal Mesh." .Obstetrics & Gynecology. 123.1 (2014): 134-39. Feiner, Benjamin, and Christopher Maher. "Vaginal Mesh Contraction." .Obstetrics & Gynecology.115.2, Part 1 (2010): 325-30.

[337] ETH. M ESH.05512280-05512314

and the "Bard Mesh" were not. Barbolt et al validated these findings in **2006**.[338] This manuscript reported on 91 Ethicon's rat study in which rats were implanted with Marlex mesh (Bard's PPPM), Surgipro PPM, VYPRO (composite PPM), and or GYNEMESH PS. Barbolt report that GYNEMESH PS "inflammation was considered to be stable at 91 days" (neither resolved nor resolving). With regard to GYNEMESH PS , it was the only mesh noted to be associated with a reduction in cellularity and a decrease of fibrosis into the pores.[339] These unique and concerning properties of GYNEMESH PS identified in 2003 and validated in 2006 (by Ethicon) were never found in the PROLIFT labels.

In **December of 2007** Johnson & Johnson (Ethicon) completed its analysis of its PROLENE, PROLENE SOFT (GYNEMESH), and ULTRAPRO meshes.[340] This analysis implanted pigs and evaluated mesh contraction and tissue integration over a 13 weeks. At 13 weeks GYNEMESH PS had contracted 27%. This was more then the 19% of PROLENE and 16% of ULTRAPRO. Although the mean contraction of GYNEMESH PS was reported to be 27%, the subcutaneous implantation of GYNEMESH PS was 35%.[341] GYNEMESH PS was also found to have a stiffness approximately 1.5 time greater than native tissue.[342] All three mesh types showed "connective tissue bridged between the mesh nodes (pores)" and the deeper implants showed very little connective tissue. This later finding is consistent with the Ethicon's GYNEMESH PS rat study that demonstrated that GYNEMESH was associated with a loss of connective tissue. The authors conclusions included, "PROLENE soft mesh (GYNEMESH PS) demonstrated the greatest amount of contraction, PROLENE mesh was intermediate, and ULTRAPRO mesh showed the least amount" and "The subcutaneous implantation site also demonstrated more connective tissue "bridging" between mesh nodes, which has historically been observed in meshes experiencing contraction". Ethicon has found that GYNEMESH PS contracts and stiffens more than two other commercially available mesh (both manufactured by Ethicon).

In 2013 Liang et al reported on concerning effects of GYNEMESH PS, Vaginal Degeneration Following Implantation Of Synthetic Mesh With Increased Stiffness.[343] The investigators implanted Gynecare PS (Ethicon), ULTRAPRO (Ethicon) or SmartMesh (Coloplast) into the vagina of 50 rhesus macaque (monkeys). The mesh-tissue complexes were excised at 12 weeks. The results are as follows:

---

338 Barbolt, Thomas A. "Biology of Polypropylene/polyglactin 910 Grafts." .International Urogynecology Journal Int Urogynecol J. 17.S1 (2006): 26-30. It is unclear if this is a reanalysis of the 2003 Ethicon rat study or a repeat study. Nonetheless, there is novel narrative and disclosure.

339 Id

340 ETH.MESH.01818397. **An Investigational Study of Swine Models to Evaluate Mesh Contraction and Tissue Integration Over a 13 Week Period**

341 Each type or mesh was implanted in two places, subcutaneous and pre-periteum implantion

342 ETH.MESH.01818397. Figure 5.

343 Liang R, Abramowitch S, Knight K, et al. Vaginal degeneration following implantation of synthetic mesh with increased stiffness. BJOG 2013;120:233-43.

> "Relative to sham and the two lower stiffness meshes, GYNEMESH PS had the greatest negative impact on vaginal histomorphology and composition. Compared to sham, implantation with GYNEMESH PS caused substantial thinning of the smooth muscle layer (1557 ± 499µm vs. 866 ± 210 µm, P=0.02), increased apoptosis particularly in the area of the mesh fibers (P=0.01), decreased collagen and elastin content (20% (P=0.03) and 43% (P=0.02), respectively) and increased total collagenase activity (135% (P=0.01)). GAG (glycosaminoglycan), a marker of tissue injury, was the highest with GYNEMESH PS compared to sham and other meshes (P=0.01)".

This study not only validated the concerning finding of Ethicon's 2003 and 2006 reports, but added even more concerning data. Implanted in a primate vagina, GYNEMESH PS, compared to other available meshes, caused muscle loss, cell death, a dramatic decrease in the natural supportive and elastic tissue of the vagina.

This same year, 2013, Feola et al reported that GYNEMESH PS implantation resulted in a uniquely high deterioration of the biomechanical properties of the vagina.[344] The objective of this study was to "Define the impact of prolapse mesh on the biomechanical properties of the vagina by comparing the prototype GYNEMESH PS (Ethicon, Somerville, NJ) to 2 new generation lower stiffness meshes, SmartMesh (Coloplast, Minneapolis, MN) and ULTRAPRO (Ethicon)". Forty-Five Rhesus monkeys underwent wither sacrocolpopexy vagina vault suspensions with one of the meshes or a sham surgery. Three months following implantation, the vaginal mesh constructs were explanted. The findings are quite concerning:

> Vaginal contractility decreased 80% following implantation with the GYNEMESH PS (p=0.001), 48% after SmartMesh (p=0.001), 68% after ULTRAPRO parallel (p=0.001) and was highly variable after ULTRAPRO perpendicular (p =0.16). The tissue contribution to the passive mechanical behavior of the MVC was drastically reduced for GYNEMESH PS (p=0.003) but not SmartMesh (p=0.9) or ULTRAPRO independent of the direction of implantation (p=0.68 and p=0.66,respectively).

The authors concluded "Deterioration of the mechanical properties of the vagina was highest following implantation with the stiffest mesh, GYNEMESH PS". This study demonstrated a dramatic decrease in important biomechanical properties of the primate vagina following GYNEMESH PS implantation and is yet another study demonstrating a loss of muscle and native cell mass or function. These negative outcomes were remarkably lower with other commercially available mesh products.

In 2015, these concerning characteristics of GYNEMESH PS were once again validated. Liang et al implanted GYNEMESH PS, (Ethicon) and 2 lower-weight, higher-porosity,

---

[344] Feola A, Abramowitch S, Jallah Z, et al. Deterioration in biomechanical properties of the vagina following implantation of a high- stiffness prolapse mesh. BJOG 2013;120: 224-32

lower-stiffness meshes, ULTRAPRO (Ethicon) and Restorelle (Coloplast) into the vagina of 49 rhesus macaque (monkeys).[345] Their findings were as follows:

- The persistent elevated ratio of collagen type III to I in the vagina 3 months after the implantation of GYNEMESH PS and ULTRAPRO Perpendicular indicates the presence of prolonged stimuli, possibly from chronic tissue injury caused by a gradual deformation/micromotion of mesh fibers under the loading conditions.
- GYNEMESH PS had a negative impact on the metabolism of both collagen and elastin—favoring catabolic reactions, whereas ULTRAPRO induced an increase only in elastin degradation. Restorelle had the least impact.

The authors concluded, "Following implantation with the heavier, less porous, and stiffer mesh, GYNEMESH PS, the degradation of vaginal collagen and elastin exceeded synthesis, most likely as a result of increased activity of MMPs, resulting in a structurally compromised tissue."

In 2003 and again in 2006 Ethicon demonstrated that its GYNEMESH PS, compared to other commercially available meshes (including those of Ethicon) was associated with uniquely adverse effects on tissue including a loss of cellularity, a decrease in fibrous ingrowth, and a remarkable tendency to erode down to and attach to muscle. Ethicon continued to sell its PROLIFT device composed of GYNEMESH PS, published no data to invalidate these findings in primates or humans, and did not update its labels to reflect its findings. In the years that followed, other investigators would validated these findings in primates and demonstrate that, compared to other commercially available meshes (included those of Ethicon), GYNEMESH PS caused remarkably more deterioration of the vaginal musculature, contractility, collagen and elastin.

From the foregoing as well as my knowledge, training, and experience, it is my opinion to a reasonable degree of medical certainty that GYNEMESH PS has a unique tendency, compared to other commercially available meshes, to erode down to and attach to muscle, has a significantly greater negative impact on the muscularity and connective tissue of the vagina with resultant loss of important biomechanical properties, this is information that would not be anticipated by either the surgeon or the patient, and Ethicon became aware of these concerns in 2003; The GYNEMESH of the PROLIFT is defective and more defective than other commercially available meshes.

EXPERT OPINION: THE PROLIFT AND PROLIFT +M DEVICES WERE DEFECTIVE IN THIER EFFECTS ON NON-TREATED COMPARTMENTS.

[345] Liang R, Zong W, Palcsey S, et al. Impact of prolapse meshes on the metabolism of vaginal extracellular matrix in rhesus macaque. Am J Obstet Gynecol 2015;212:174.e1-7.

In an ideal situation, the treatment of one compartment should have no negative effect on another. The development of POP in one compartment after treatment of another compartment is referred to as untreated or non-treated compartment failure. The low rate of untreated compartment failure following native tissue surgery can be explained by the natural progression of pre-existing mild prolapse. PROLIFT devices are associated with a high rate of untreated compartment failure, more than double of native tissue surgery.[346] Ethicon knew of this problem as it stated in a PROLIFT label, "the side untreated with mesh may be prone to failure as it takes a greater percentage of the valsalva forces over time".[347] This is perhaps most easily understood by the basic physical formula for pressure, Pressure = Force / Area. If force is exerted over a large area, pressure is less. When a portion of the normal elastic tissue of the vagina is replace by a non-elastic rigid plastic (degraded and contracted GYNEMESH PS), the area of the remaining elastic vagina is decreased and therefore exposed to a greater pressure. More pragmatically and for demonstration purposes, one can push on a watermelon with their palm all day long and not make a dent. However, if we take that same amount of pressure and concentrate it on a tiny area, say the tip of a screwdriver, the watermelon is immediately puncture. Regardless of the science or formula that explains the complication, the rigid, non-compliant PROLIFT implants dramatically increase the rate of nontreated compartment failure and associated reoperation.[348]

From the foregoing as well as my knowledge, training, and experience, it is my opinion to a reasonable degree of medical certainty that the PROLIFT and PROLIFT +M devices caused an increase in the rate of untreated compartment failure, this is information that would not be anticipated by either the surgeon or the patient, and Ethicon was ware of this information; The PROLIFT and PROLIFT +M methods are defective in their effects on the untreated compartments.[349]

EXPERT OPINION: THE PROLIFT and PROLIFT +M METHOD WAS DEFECTIVE

The novel armed-mesh, blind-trocar pass method of PROLIFT created novel complications. Prior to the introduction of PROLIFT to the market, all transvaginal mesh surgery was being performed by direct fixation to pelvic tissues. The surgeon would dissect a pathway to a fixation point. While touching this point of attachment with their finger, surgeons would secure the mesh with a suture. The PROLIFT method required a blind passage of a long trocar (similar to a long curved screw

---

[346] Withagen M, Milani A, de Leeuw J, Vierhout M. Development of de novo prolapse in untreated vaginal compartments after prolapse repair with and without mesh: a secondary analysis of a randomised controlled trial. BJOG 2012;119:354–360.

[347] ETH.MESH.00658268 (PROLIFT SURGEONS RESOURCE MONOGRAPH)

[348] See the Clinical Data and Related Correspondence section for the review of the literture.

[349] Available to Ethicon in its 2006 TVM data and elsewhere in both retrospective and prospective studies of its investigators and consultants. See also THE CLINICAL DATA and ASSOCIATED COMMUNICATIONS of this report.

driver) as a substitution for meticulous dissection to the area of fixation. Additionally, when executed uneventfully, the trocars would blindly penetrated through muscles and soft tissues often within millimeters of vital nerves, blood vessels and organs leaving the novel mesh arms within muscle bellies in close approximation to these structures. Chen et al demonstrated that TVM method (PROLIFT) results in the passage of trocars only millimeters from the obturator blood vessels, rectal blood vessels, bladder and rectum.[350] Unfortunately, in some cases, the trocars would injure these nerves, blood vessels and organs resulting in severe morbidity. Ethicon, identified the potential for such grave complications, prior to marketing PROLIFT, during its GYNECARE PROLIFT Design Validation. In its design validations study report, Ethicon noted that the cannula tip gets "lost" in deep tissue. With regard to such, Ethicon explained that "This statement indicated that the surgeon had difficulty tactilely feeling the tip of the cannula during use, not that a portion of the device is left behind during insertion". Translated for someone who has not performed or seen a PROLIFT procedure: The surgeon is passing the big pointy curved screwdriver like device through the pelvis and trying to aim it at his or her finger inside the vagina, but the surgeon is having trouble aiming the trocar so that the point tip exits at his or her finger. If the trocar exits elsewhere, that means its course through the pelvis was not as intended. The complications of such will be discussed shortly.

The self-tailored (trimmed to the patient anatomy) and directly fixated vaginal mesh surgery that predated the PROLIFT (TVM) did not pull mesh through the levator ani and obturator muscles of the pelvis. This surgery did not pull mesh around the rectum. Hence, the material defects of the mesh resulted in comparatively less complications. The introduction by Ethicon of its novel 4-armed, blind-trocar passing, "Tension Free Mesh" (TVM) surgery introduced both a higher incidence of known mesh complications and serious, often untreatable novel complications. As discussed elsewhere in this report, Ethicon recognized this issue. A group of Ethicon's paid consultants and employees, including its World Wide Medical Director of reported, "However, the introduction of vaginal graft augmentation with the use of trocars has introduced new complications that are not associated with traditional repairs, such as extra-pelvic infections and mesh contraction, which cause pelvic and vaginal pain that often require further surgery".[351] Ethicon was the company that introduced the novel, armed, blind-pass, trocar to the world. Indeed, the method was so novel that it was granted both U.S. and international patents.

As noted by Ethicon's World Wide Medical Director and consultants, and as is consistent with my experience with over 1000 mesh implantations and ongoing management of complications, the novel method introduced novel complications including extra-pelvic infections and mesh contraction which cause pelvic and vaginal

---

[350] Chen CCG,Gustilo-Ashby AM, Jelovsek JE, et al. Anatomic relationships of the tension-free vaginal mesh trocars.Am J Obstet Gynecol 2007;197:666.a1-666.a6.

[351] Zyczynski HM, Carey MP, Smith ARB, et al. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:587.e1-8.

pain that often require surgery. This should not be surprising even to one not skilled in the art of surgery or anatomy. Prior to the introduction of PROLIFT, acute inflammation, chronic inflammation, infection, and contraction associated with transvaginal mesh surgery was confined to the place of surgery, the vagina. The PROLIFT device and method pulled all these problems out of the pelvis, by definition, pulled all of these problems through the muscles of the pelvis, around the bladder and rectum, and into the groin and buttock. Here is a short list of some theses new problems that began to appear:

- Mesh contraction around the rectum causing rectal pain and constipation.
- Mesh inflammation and contraction and scaring in or around the anus causing fecal incontinence.
- Mesh eroding into the rectum causing pelvic infection and or rectovaginal fistula (with stool passing though the vagina).[352]
- Trocars and or mesh arms pulled through the rectum resulting in pelvic infection and or rectovaginal fistula (with stool passing though the vagina).
- Mesh arm contraction pulling on sacrospinous coccygeus muscle complex and causing mild to severe pudendal nerve related pain (pelvic pain, pain with sitting, parasthesia along the dermatome of the nerve).
- Pudendal vessel laceration with hemorrhage and blood transfusion
- Buttock and ischial rectal fossa abscess often requiring open drainage
- Buttock cellulitis
- Mesh arms or body residing in bladder muscle often resulting in lower urinary tract symptoms (The method of PROLIFT encouraged deeper dissection leaving the GYNEMESH PS, a mesh prone to deep erosion and muscle fixation, close to or inside the bladder muscle).
- Mesh arms inside the bladder resulting in lower urinary tract symptoms, infection, and stones.
- Adductor space complications of the groin and leg including pain with ambulation, difficulty with ambulation, pain with leg adduction during coitus, adductor space infection and abscess, and groin cellulitis.[353]
- Obturator space complications including obturator vessel injury and hemorrhage and transfusion, obturator nerve injury with resultant gate problems, obturator space infection and abscess.[354]
- Vaginal banding[355]

Some of these new mesh related complications such as buttock, groin and pelvic pain were quite common with RCT related reports reaching 10% and case series reports ranging from 2.9 to 18.3%.[356] Although my person experience has witnessed the

[352] Rectal injuries did occur with self tailored mesh surgery. However, these were typically during dissection and lead to non-placement of the mesh.

[353] Although adductor space complications were also known to the transobturator sling, these complications were unknown to prolapse surgery. Furthermore, the ramifications were different as the size of the implant was many times larger.

[354] Id

[355] This problem was well recognized by both Ethicon and its key opinion leaders. ETH-48281

[356] Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse. Committee Opinion. Number 513. December 2011. Obstet Gynecol. 2011 Dec;118(6):1459-64. doi: 10.1097/AOG.0b013e31823ed1d9.

lower side of this range, this is still common. With regard to vaginal banding created by the anterior PROLIFT, Ethicon product director, Scott Jones reported "Regardless of how doctors adjust mesh, there is still a definite ridge or banding that can be vaginally palpated..".[357] Having performed over 1000 mesh implantation surgeries and having treated many women for complications of PROLIFT and PROLIFT +M, I have found the majority of these complications to occur in a 2-3% of patients. However, the as a result of constellation of new complications, it is has been my experience that at least 1-10 women experiences on of the less common complications. By way of example, Ethicon disclosed 6.3% pelvic pain and 2.3 % bladder perforation rates for its early interim PROLIFT +M RCT.[358] The problem with these novel complications is much greater then one might estimate based on the reported incidences. These problems are uniquely difficult to treat and often untreatable.

Many if not all of the above noted novel complications caused by PROLIFT are associated with passage of the mesh arms. Whereas a surgeon can treat a self-tailored mesh complication through a simple vaginal incision (the same incision made for the original surgery), a vaginal incision does not offer any access to the arms of a PROLIFT implant. The PROLIFT arms are pulled, blindly, through deep tunnels created by the PROLIFT trocars. In order to get access to the arms, a surgeon needs to make new incisions in the buttock and or groin. After making these new extra-pelvic incisions, the surgeon then needs to dissect through either the adductor (groin) and obturators spaces (for anterior PROLIFT) or the perianal and ischiorectal spaces (for posterior PROLIFT). These spaces, with their associated large and small blood vessels and nerves, are poorly understood by the overwhelming majority of surgeons. These surgical dissections are not trained in residency programs. Even those few expert surgeons who are willing to attempt these dissections are often caused to abandon such attempts (secondary to fear of creating injury). This makes many of the novel mesh complications untreatable.

Ethicon commissioned a physician survey that questioned surgeons on the technical challenges of PROLIFT. The responses are particularly relevant to the methodological defects.[359]

"The following were mentioned most often by these physicians as the key technical challenges of PROLIFT:
- blind passage (25%)
- knowledge of anatomy (15%)
- high level of surgical skill required (15%) - not over tightening the mesh (10%)
- dissection (10%)"

"Here is some of what they said about the technical challenges of PROLIFT":

---

[357] ETH-48281

[358] ETH.MESH.07724613

[359] ETH.59497

"You must know the anatomy. If you don't, you don't have any business doing it. It's a blind technique."
"PROLIFT takes skill. It's not for every surgeon."
"PROLIFT is not for everybody. The challenges are that it requires a high comfort level with the anatomy and blind passage."
"It requires blind passage and a different type of dissection." "The biggest challenge is the blind passage avoiding vessels and nerves."

The transvaginal implantation of PROLIFT favors bacterial contamination with resultant potentiating of the GYNEMESH material defects. The vulvar skin is the home of numerous bacteria including staphylococcus, streptococcus, lactobacillus and even MRSA and clostridium. These bacteria are harmless when living on the skin, but can cause grave complications and even death when introduced into the body. The method advocated by PROLIFT and PROLIFT +M for the implantation of its GYNEMESH PS and ULTRAPRO meshes causes the surgeon to push a trocars (screwdriver sized needles) through the perineum and or vulvar skin and exit these needles through a vaginal incision. These needles are hence exposed to dangerous bacteria on the skin and carry such bacteria through all the tissues within the pelvis. The PROLIFT mesh is then attached to the potentially contaminated needles, pulled through the already "clean contaminated vagina" and carried back through the contaminated tract created by the needles, eventually exiting through the skin. As one can easily see, both the tissues and the mesh are at high risk of contamination with dangerous and deadly bacteria. Peroxides and acid produced by Lactobacillus as well as the oxidative chemicals released by inflammatory cells leads to degradation, contraction, and clinical infection. Contamination of transvaginal mesh has been shown in several demonstrated by several investigators. For example, in 2008, one report of bacterial analysis of mesh explants by Boulanger showed that bacterial contamination existed to some degree on every explant. In another from 2009, Vollebregt took swab cores from implanted mesh during surgery.[360] Over 83% of the 67 samples taken were positive for contamination by vaginal bacteria. Such contamination, they concluded, occurs frequently. In 2010, Mamy et al demonstrated the association between bacterial contamination and contraction. [361] These investigators found infected mesh to contract 4 times more than non-infected mesh. Thus, it is clear that the transvaginal mesh implantation method is inherently flawed as the majority of implants shall become contaminated with bacteria capable of degrading the implant. In addition to the effects of bacteria on the material properties of the mesh, the risks of infection are well established. Indeed the ongoing tort has revealed a growing number of women who have suffered from severe mesh infections associated with pathogenic skin bacteria.

---

[360] Boulanger, Loïc, Malik Boukerrou, Chrystèle Rubod, Pierre Collinet, A. Fruchard, René J. Courcol, and Michel Cosson. "Bacteriological Analysis of Meshes Removed for Complications after Surgical Management of Urinary Incontinence or Pelvic Organ Prolapse.". International Urogynecology Journal Int Urogynecol J. 19.6 (2008): 827-31. Vollebregt, Astrid, Annet Troelstra, and C. Huub Van Der Vaart. "Bacterial Colonisation of Collagen-coated Polypropylene Vaginal Mesh: Are Additional Intraoperative Sterility Procedures Useful?" International Urogynecology Journal Int Urogynecol J 20.11 (2009): 1345-351.

[361] Mamy, Laurent, Vincent Letouzey, Jean-Philippe Lavigne, Xavier Garric, Jean Gondry, Pierre Mares, and Renaud De Tayrac. "Correlation between Shrinkage and Infection of Implanted Synthetic Meshes Using an Animal Model of Mesh Infection." International Urogynecology Journal Int Urogynecol J 22.1 (2010): 47-52.

From the foregoing as well as my knowledge, training, and experience, it is my opinion to a reasonable degree of medical certainty that the PROLIFT and PROLIFT+M methods caused novel extra-pelvic complications that are difficult or impossible to treat, were uniquely prone to complications, that such complications were common, that the PROLIFT and PROLIFT+M methods caused an increased incidence of non-novel complications that were uniquely difficult or impossible to treat, that these novel and non-novel complications represented a substantial increase in POP surgery morbidity and disability to women and harmed their families, this is information that would not be anticipated by either the surgeon or the patient, and Ethicon was ware of this information; The PROLIFT and PROLIFT+M methods are defective.

EXPERT OPINION: SAFER ALTERNATIVES EXIST[362]

Traditional native tissue POP surgeries provide equal anatomic cure rates in the treatment of apical POP and posterior POP. Although systematic reviews of the literature suggest that transvaginal mesh may provide an anatomic, but not quality of life, benefit in the anterior compartment, such reports reflect a meta-analysis of pooled mesh data. Ethicon's PROLIFT data does not support that argument. Regardless, native tissue surgeries provide, at a minimum, equivalent quality of life benefits with lower complication rates. In comparison to transvaginal mesh surgery, the historical sacrocolpopexy has been shown to be a safer, more effective method of treating apical POP that results in higher patient satisfaction.

There was even safer transvaginal mesh alternatives. Ethicon had proven that its PROLENE mesh was safer than its GYNEMESH and ULTRAPRO. Ethicon had also proven that its ULTRAPRO was safer than its GYNEMESH. Other meshes such as Bard's mesh and Coloplast's Smartmesh and Restorelle had been shown to be safer than GYNEMESH PS. Hence, even in a make-believe world in which native tissue repairs and Sacrocolpopexy did not exist, Ethicon could have decreased many complications by using a safer mesh product. Although it eventually introduced PROSIMA +M for this reason, there were other meshes shown to be safer and it continued to sell PROLIFT (GYNEMESH PS). Also, the use of self-tailored directly fixated mesh would remove the large group of trocar and arm related complications.

I have not performed a transvaginal mesh implantation in over 6 years. In this time frame I have performed hundreds of native tissue colporrhaphies, colpopexies, and sacrocolpopexies. I have observed neither a single native recurrence beyond the hymenal ring or a single symptomatic recurrence. With the exception of urinary tract

[362] The opinions of this section are substantiate by the pool of relavent medical literature covered in the Clinical Data section of this report.

infections, I have noted only two complications.[363] These findings of high efficacy and safety have been validated by a re-analysis of historical data that, originally, focused on anatomic rather than symptomatic outcomes.

From the foregoing as well as my knowledge, training, and experience, it is my opinion to a reasonable degree of medical certainty that numerous safer alternatives to PROLIFT and PROLIFT +M.

The PROLIFT and PROLIFT+M LABELS WERE INADEQUATE

This section shall not include a discussion of misbranding or other violations of the law. Label deviations from FDA guidelines are covered in the report section titled REGULATORY COMPLIANCE AND NONCOMPLIANCE

EXPERT OPINION: THE INSTRUCTIONS FOR USE WERE INADEQUATE

2004 IFU: ETH.MESH.02341522
2010 IFU: ETH.MESH.02341658

Instructions for use (IFU), in any industry, exist to allow the customer to use a product safely and effectively. Conventional medical industry standards dictate that an IFU provide that the IFU will not only teach safe and effective use, but will also provide appropriate cautions, warnings, uncertainties, contraindications, the meaningful material facts, do so without ambiguity, and be included with the device. In the medical device world, surgeons consider the IFU to be an honest and factual document that is void of trade puffery, misleading information, and marketing narrative. Although the FDA guidelines my have contributed to the development of this historical standard, this is not relevant to the expectations of the surgeons, an expectation known by manufacturers.

1. The 2004 IFU states, "Refer to the recommended surgical technique for the GYNECARE PROLIFT Pelvic Floor Repair Systems for further information on the GYNECARE PROLIFT procedures". However, this document was not included with the device. The IFU does not teach how to use the device safe and effectively but refers to another document, a document that is not include. The IFU is hence inadequate. By way of example, a surgeon, from time to time, may forget an essential step or component of new procedure. It is not uncommon for the surgeon to ask the operating room nurse to look in the IFU. This would not work for PROLIFT as the IFU referred to a missing document. Additionally, it does not state where a surgeon could find this document. Although the 2010 IFU is updated and informs the surgeon he can contact a

[363] Both after robotic Sacrocolpopexy: One partial SBO that resolved with bowel rest and one that resolved with the laparoscopic lysis of a single adhesion.

sales representative for this document, the document is still missing and the IFU remains inadequate.

2. The 2004 and 2010 IFUs **DESCRIPTION** of the mesh, GYNECARE GYNEMESH PS is inadequate for multiple reasons. It provides information that is non-factual, misleading, and is a marketing narrative. It states, "The mesh affords excellent strength, durability, and surgical adaptability, with sufficient porosity for necessary tissue ingrowth". As noted elsewhere in this report, the mesh became contracted, and brittle. Furthermore, Ethicon new its mesh contained numerous pores that were not sufficient for ingrowth yet favored bridging fibrosis and contraction. It states "The mesh is knitted by a process which interlinks each fiber junction and which provides for elasticity in both directions" and "The bi-directional elastic property allows adaptation to various stresses encountered in the body." Yet, once implanted, there is almost a complete loss of elasticity. These statements were not included in the 2010 IFU.
3. The 2004 and 2010 IFUs **PERFORMANCE** paragraph is inadequate for multiple reasons. It provides information that is non-factual, misleading, and is a marketing narrative. It states, "Animal studies show that implantation of GYNECARE GYNEMESH PS mesh elicits a minimum to slight inflammatory reaction, which is transient and is followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, thus incorporating the mesh into adjacent tissue". Yet, as discussed at length elsewhere in this report, Ethicon had conducted animal studies that demonstrated that the inflammation was not transient, the mesh became covered by bridging fibrosis, and was associated with loss of connective tissue. Multiple other investigators also demonstrated this. This section paragraph also included, "The mesh remains soft and pliable, and normal wound healing is not noticeably impaired". Not only does the mesh become hard and brittle, but impaired wound healing was one of the greatest frustrations known to Ethicon, its TVM investigators[364], and other mesh manufacturers, whom reported that such contributed to the high rate of mesh extrusion. Indeed, the trade invented a term to describe this "Persistent Delayed Healing". Also included is the statement "The material is not absorbed, nor is it subject to degradation or weakening by the action of tissue enzymes". The degradation and weakening of polypropylene mesh is well known to both material scientists and Ethicon.[365]
4. The 2004 IFU **WARNINGS AND PRECAUTIONS** section states "Transient leg pain may occur and can usually be managed with mild analgesics". This teaching is ambiguous in that it does not define "temporary". This warning is also fails to teach that leg pain may not be transient and how such non-transient leg pain should be managed. Leg pain is typically caused by irritation

[364] "These problems (mesh extrusion) arise due to exposure of the mesh material caused by inadequate healing". Collinet, Pierre, Franck Belot, Philippe Debodinance, Edouard Ha Duc, Jean-Philippe Lucot, and Michel Cosson. "Transvaginal Mesh Technique for Pelvic Organ Prolapse Repair: Mesh Exposure Management and Risk Factors." .International Urogynecology Journal Int Urogynecol J</i> 17.4 (2005): 315-20.

[365] DEGRADATION CITATIONS (PUT ALL 11 HERE)

of the pudendal nerve (arms of the PROLIFT and PROLIFT+M posterior device). Pain secondary to hematoma and surgical irritation typically mild to moderate and resolves begins to improve within days. However pain from proximity of the mesh arms to the nerve, through the nerve sheath, or contraction of the mesh around the nerve does not typically improve. This pain is usually moderate to severe and often worsens. If a surgeon intervenes within the first 24 to 48 hrs, the mesh can sometimes be removed. However, the possibility of removing the mesh becomes increasingly difficult or impossible in the days and weeks that follow. The 2010 IFU contains multiple warnings and precautions that were missing from the 2004 IFU. Hence, the 2004 IFU did not disclose important warnings including, "A digital exam should be performed to detect possible rectal injury", Cystoscopy may be performed to confirm bladder and ureteral integrity", "Do not affix the GYNECARE GYNEMESH PS mesh implant with any staples, clips, or clamps as mechanical damage to the mesh may occur", and "If the Mesh implant is used in contaminated areas, it must be with the understanding that subsequent infection may require its removal". The absence of these warnings likely resulted in great morbidity including rectal pain, rectovaginal fistula (with stool coming out of vagina), vesicovaginal fistula (with urine coming out the vagina), infection, abscess, and other bowel and bladder problems. Not only did the 2004 IFU fail to provide important warnings and cautions, it actually taught the user to violate a precaution. The 2004 IFU provided instructions for placing staples and other fixation device. Yet the 2010 IFU specifically taught against this.[366]

5. The 2010 IFU **WARNING** section contained the same misguidance about transient leg pain. The 2010 IFU **PRECAUTIONS** section stated ""If the Mesh implant is used in contaminated areas, it must be with the understanding that subsequent infection may require its removal". This is an ambiguous warning that teaches a dangerous practice. The vagina is incsions is always considered a "clean-contaminated wound". Hence, it is unclear if this precaution applies to every PROLIFT implant. It is a deviation of the standard of care to place any implant in a contaminated wound. This precaution suggests that PROLIFT devices may be implanted in a contaminated wound. Finally, this warning suggests that the PROLIFT device can be removed. Ethicon and its TVM group of expert consultants knew that complete removal of the PROLIFT devices was rarely if ever possible.
6. The 2004 AND 2010 IFUs did not provide warnings or precautions with regard to adverse events and complications known to Ethicon including cannula damage during loading (that could cause harm to device and patient), accidental removal or displacement of the cannula, or placement under too much or insufficient tension. Ethicon's internal documents indicate that it was aware of these problems and intended to disclose such and teach appropriate responses to such in its IFU. [367]

[366] ETH.MESH.02341526

[367] ETH.07248-07303

7. The 2004 IFU **ADVERSE REACTIONS** section states "Potential adverse reactions are those typically associated with surgically implantable materials, including infection potentiation, inflammation, adhesion formation, fistula formation, erosion, extrusion and scarring that results in implant contraction". This statement is incorrect as it indicates that the adverse reactions of transvaginal implantation of GYNEMESH PS are the same as implantation of biologic grafts and or absorbable grafts and or non-polypropylene synthetic meshes, and or other synthetic meshes. As demonstrated by the rat and pig studies of Ethicon and the large pool of medical and scientific literature, the adverse reactions of these other materials are quite different (and typically more mild and more transient). Ethicon's rat and pig studies had even demonstrated that the adverse reactions associated with GYNEMESH PS were different than those associated with other Ethicon PPM products. It is important to remember that Ethicon target market included users of biologic grafts and other PPM products. Additionally, this IFU statement suggests that the adverse reactions of the transvaginal implantation of GYNEMESH PS are the same as those associated with the implantation of these different materials in the abdomen or elsewhere. Many surgeons were not familiar with the adverse reactions of materials implanted in the vagina, but were familiar with implants used elsewhere in the body. Clearly the adverse reactions associated with dental implants, joint implants, and even hernia mesh implants are not the same as those of transvaginal GYNEMESH PS. Additionally, the 2004 IFU failed to disclose important adverse reactions that later appeared in the 2010 IUF: "Potential adverse reactions are those typically associated with pelvic organ prolapse repair procedures, including pelvic pain or pain with intercourse. These may resolve with time" and "Dissection for pelvic floor repair procedures has the potential to impair normal voiding for a variable length of time".
8. The 2010 IFU **ADVERSE REACTIONS** section amended the ""Potential adverse reactions are those typically associated with surgically implantable materials….." statement of the 2010 IFU to now stating "Potential adverse reactions are those typically associated with surgery employing implantable materials of this **type**". As noted above, even this statement is not true. Ethicon's own studies had demonstrated the adverse reactions of its GYNEMESH PS were unique. Ethicon's studies had demonstrated GYNEMESH PS to be associated with greater contraction, more tissue destruction, and erosion down to and adherence to muscle. These findings were later validated by other investigators. The 2010 IFU ADVERSE REACTION section also added, "Potential adverse reactions are those typically associated with pelvic organ prolapse repair procedures, including pelvic pain or pain with intercourse. These may resolve with time." The growing and now large pool of retrospective data from Ethicon's paid consultants and numerous other investigators as well as Ethicon's prospective data demonstrated that this statement was far from the truth. By way of example, native tissue surgeries are not associated with devastating trocar related injuries of the obturator, pudendal, and rectal blood vessels, the severe morbidity of mesh contraction,

or the any of the long list of novel trocar and mesh related complications discussed elsewhere herein. Indeed, PROLIFT related adverse reactions were not even those typical of self-tailored no blind-pass mesh and biologic graft POP surgeries. This is very misleading to surgeons migrating or considering migration from to PROLIFT POP surgery.

9. The 2010 IFU CLINICAL PERFORMANCE paragraphs included numerous inaccurate and misleading statements.

- "The primary effectiveness endpoint for both studies was the proportion of subjects for whom **correction of prolapse** was achieved (ICS Stage 0 or I) evaluated at 12 months post-operatively". This is an inaccurate statement that directs attention away from the failure of the study. The primary endpoint as stated in Ethicon's study protocol was "Effectiveness of the TVM treatment in curing vaginal prolapse as indicated by the twelve-month **failure rate**". As noted elsewhere in this report, the study failure rate exceeded 20% and the study was deemed a failure.
- "Study populations available for follow-up at 12 month were 83 patients in the US and 87 patients in France with a median patient age of 62 and 66.5, respectively". This statement fails to disclose an important material fact. Study populations were, at this time available for many years. Indeed, the last patient was completed five years earlier, in January of 06. Three-year data from the French cites had been available since 2008. Yet Ethicon leads the user to believe that "this is all we have so far". This data was more concerning and conspicuously absent.
- "The 12-month postoperative study results were as follows (US, France): proportion of subjects with ICS Stage II or greater (12.0%, 18.4%), met pre-defined criteria of upper limit of 90% CI less than 20% (yes, no)…". This statement does not disclose the material facts and disguises disclosed facts. It neither discloses the upper limits of the confidence intervals nor discloses the fact that the studies were failures. This statement in no way effectively communicates to a device user the material facts: An upper limit CI of greater than 20% deemed the study a failure. The French study hit 26.6% and was a failure. The U.S. study hit 19.6%. Additionally, Ethicon's study protocol had indicated that a recurrence rate of 13% would be a failure.[368]

From the foregoing as well as my knowledge, training, and experience, as a surgeon, as CEO and COO of medical device companies, and as a labeling consultant to medical device companies, it is my opinion to a reasonable degree of medical and corporate certainty that the PROLIFT IFUs were inadequate by medical industry standards, standards known to Ethicon and expected by surgeons.

[368] ETH.MESH.00401365

EXPERT OPINION: THE GYNECARE PROLIFT PELVIC FLOOR REPAIR SYSTEM-SURGICAL TECHNIQUE[369] WAS INADEQUATE

Conventional medical industry standards dictate that corporately developed and disseminated technique guides, user manuals, and the like will not only teach safe and effective use but will do so without ambiguity. It is also important to remember that this label is the label users are referred to by the PROLIFT IFUs.

- "This will dictate that the bladder dissection be performed through the pericervical incision". This teaches the user to place the PROLIFT anterior by dissecting, retrograde, through the hysterectomy incision. Not only had this method already been shown to be associated with a dramatic increase in the risk of mesh extrusion (erosion) (Odds Ratio of 5). [370]Even more concerning, elsewhere in the label it states "Alternatively, a sagittal anterior colpotomy starting at the vaginal incision and ending approximately 1 cm from the bladder neck could be used if needed." This is also referred to as a "T-incision", an incision associated with an even greater risk of mesh extrusion (Odds Ratio of 6).[371] Strangely, in a different section of the label it warns against this incision. "The principles regarding vaginal incisions include minimizing the size of the vaginal incisions and avoiding T-shaped incisions. The teachings provided herein are in conflict and, by definition, create ambiguity. Furthermore, these teachings an unsafe method. Indeed, Ethicon's label, PROLIFT Surgeon's Resource Monograph (PSRM) teaches "Simultaneous hysterectomy is associated with a significant increase in anterior mesh exposure, especially when the 2 incisions are contiguous".[372]
- The paragraph entitled Mesh Fixation states "**additional stitches may be used** along with the straps to aid in proper placement of the Implant". The very next paragraph, Vaginal Preservation, states "**It is recommended to avoid** large vaginal excisions and **fixation** of the vagina to the implant". Several pages later it states "Additional fixations remain optional" and gives instructions on how to fixate the mesh, "In the event that sutures, staples, or other fixation: devices are used in conjunction with the mesh, it is recommended that they be placed at least 6.5 mm (1/4") from the edge o f the mesh." These are contradictory statements that create ambiguity.
- "If required, small reductions in the dimensions of the Total Implant to ensure proper fit should be performed at this point". This statement discourages trimming of the graft to fit the patient. As discussed elsewhere in this report,

---

369 ETH.MESH.03960103

370 Collinet, Pierre, Franck Belot, Philippe Debodinance, Edouard Ha Duc, Jean-Philippe Lucot, and Michel Cosson. "Transvaginal Mesh Technique for Pelvic Organ Prolapse Repair: Mesh Exposure Management and Risk Factors." .International Urogynecology Journal Int Urogynecol J. 17.4 (2005): 315-20

371 Id

372 ETH.MESH.00658368

one size does not fit all. Furthermore, Ethicon's PSRM label states, with regard to decreasing the incidence of mesh complications, "The best prevention is strict adherence to the surgical technique guidelines with full-thickness incision, good tissue handling, no vaginal trimming, tension-free wound closure and keeping the mesh flat and tension free". Clearly "small reductions in the dimensions" will, in many instances, not allow on to keep the mesh flat.[373] This instruction of the guide does not encourage the safe use of PROLIFT and is ambiguous as it is contradictory to the "keeping the mesh flat" teachings of the PSRM label.

- Numerous statements are made that indicate that the PROLIFT mesh should be placed "tension free". Examples include:
    - "These implants are designed to cover all existing or potential pelvic floor defects in a tension free way".
    - "The straps should be used to make any required additional fine adjustment to implant position, taking care to not place the mesh under tension".

  However, no instructions are provided on how to place the mesh in a tension free way. Indeed, there are additional instructions that increase the risk of creating tension; "Further fine adjustment of the tension and position of the Total Implant may be performed following closure of the vaginal incisions at the end of the procedure". This instruction encourages the user to pull on the mesh arms, altering the tension, after the incision is closed, at a time when there is no ability to see the body of the mesh. The teachings of Ethicon here in are ambiguous and do not provide for the safe and effective use of its PROLIFT devices.

From the foregoing as well as my knowledge, training, and experience, as a surgeon, as CEO and COO of medical device companies, and as a labeling consultant to medical device companies, it is my opinion to a reasonable degree of medical and corporate certainty that THE GYNECARE PROLIFT Pelvic Floor Repair System-SURGICAL TECHNIQUE label was inadequate by medical industry standards, standards known to Ethicon and expected by surgeons.

EXPERT OPINION: THE GYNECARE PROLIFT SURGEON'S RESOURCE MONOGRAPH[374] WAS INADEQUATE

Conventional medical industry standards dictate that corporately sponsored and disseminated device guidance and the like will not only teach safe and effective use but will do so without ambiguity, disclose uncertainties and the presence of conflicting opinions, and be void of marketing narrative. Indeed, this label states

---

373 See Figure 6, photograph from Svabík, Kamil, Alois Martan, Jaromir Masata, Rachid El-Haddad, Petr Hubka, and Marketa Pavlikova. "Ultrasound Appearances after Mesh Implantation—evidence of Mesh Contraction or Folding?" International Urogynecology Journal Int Urogynecol J 22.5 (2010): 529-33.

374 ETH.MESH.00658363-400

"….even single cases out of the large number of total GYNECARE PROLIFT System procedures performed are honestly presented", suggesting to the reader that this label provides an honest and complete representation of the material facts. Such is not the case.

- "Many surgeons are finding that it has lower rates of dyspareunia than historical procedures such as the posterior colporrhaphy. The available early cases support this notion". Not only does this statement fail to disclose that conflicting expert opinions exist, it does not disclose the inventor of the TVM method presented conflicting data. It also an inaccurate representation of the material facts. Early cases did not support the notion. Indeed, PROLIFT had been on the market for years before the first RCT compared PROLIFT to historical procedures. This inaccurate and incomplete statement of lower dyspareunia rates represents a marketing narrative.
- "Infection rates have been exceptionally low and only typical antibiotic prophylaxis is required". Ethicon's 2006 prospective TVM studies found a 22% rate of urinary tract infections. Although "exceptionally low" is ambiguous, 22% is not an exceptionally low rate of infection by any definition.
- "In addition, while hysterectomy complications are uncommon in experienced hands, they represent the majority of complications seen with this procedure". This is not correct and is misleading. Hysterectomy has been associated with an increased risk of mesh exposure (extrusion). However, mesh exposure is only one of many complications associated with PROLIFT and uterine conservation does not decrease the rate of the majority of complications. Indeed, all complications, including mesh exposure, occur commonly in the absence of hysterectomy. As covered in the Clinical Data section of this report, mesh extrusion is extremely common in the absence of hysterectomy. Withagen et al prospectively demonstrated a 12% of PROLIFT mesh extrusion in the absence of hysterectomy.[375] Furthermore, none of the commonly reported PROLIFT complications were absent from this study. This statement reference herein misleads the user to believe that the majority of complications can be avoided by avoiding hysterectomy. Additionally, it misleads the user with the inaccurate statement that PROLIFT complications associated with hysterectomy are uncommon in experienced hands. A group of Ethicon's TVM investigators including the inventor of the TVM method experienced a 11.5% rate of mesh extrusion when performing a hysterectomy at time of PROLIFT.[376]
- "While inexperienced surgeons initially may look for smaller pieces of mesh, the larger piece of mesh is necessary to prevent bearing down on the vaginal capacity during healing. "Anteriorly, small amounts of individualizing can be done". This teaching discourages trimming the mesh to whatever size is

[375] Withagen, Mariëlla I., Mark E. Vierhout, Jan C. Hendriks, Kirsten B. Kluivers, and Alfredo L. Milani. "Risk Factors for Exposure, Pain, and Dyspareunia After Tension-Free Vaginal Mesh Procedure.". Obstetrics & Gynecology. 118.3 (2011): 629-36.

[376] Caquant, Fréderic, Pierre Collinet, Philippe Debodinance, Juan Berrocal, Olivier Garbin, Claude Rosenthal, Henri Clave, Richard Villet, Bernard Jacquetin, and Michel Cosson. "Safety of Trans Vaginal Mesh Procedure: Retrospective Study of 684 Patients." .Journal of Obstetrics and Gynaecology Research</i> 34.4 (2008): 449-56.

necessary to allow it to lay flat. Yet, elsewhere in the Monograph it teaches, in order to "keeping the mesh flat" will reduce complications. The teaching herein is conflicting and, by definition, ambiguous and decreases safety.

- "The collagen-dominant layer that invests the mesh will contract over time and cause an estimated 10-20% contraction". This statement is a blatant misrepresentation of the material facts. Not only does the overwhelming majority of the medical and scientific literature demonstrate a range of contraction that is dramatically higher than this, Ethicon's animal data demonstrated a 27% to 35% contraction at only 13 weeks post-implantation. As mesh contraction has been reported to be as high as 85%, this overt misrepresentation of the material facts represents a marketing narrative.
- The Technical Pearls section of the Monograph states "The design of the trocar allows for surgeons to pass the mesh through the actual sacrospinous ligament posteriorly and immediately adjacent to the ischial spine on the deep anterior pass. This is a teaching that encourages great morbidity and potential fatal injury. The pudendal complex (artery, vein and nerve) and sciatic nerve are located anywhere from 0.90 to 3.30 cm medial to the ischial spine.[377] Although later in the same paragraph the Monograph provides a contradictory teaching, "When placing the posterior GYNECARE PROLIFT System cannulas through the sacrospinous ligament, stay 2-3 centimeters medial to the spine to reduce any potential of nerve injury" this still falls directly within the region of these vital anatomic structures. In addition, the teaching of these "Technical Pearls" is in direct conflict to the safer teaching provided by the PROLIFT PELVIC FLOOR REPAIR SYSTEM-SURGICAL TECHNIQUE label that states, "The device is advanced until it is in contact with the inferior side of the sacrospinous ligament approximately 3-4 cm medial to the ischial spine". The teachings of the Technical Pearls are ambiguous and teach away from safety.
- "The incidence of bladder or ureter injury is likely to be exceptionally low but is significantly more morbid if missed before leaving the operating room". Yet Ethicon had RCT demonstrating its method was associated with over a 2% incidence of bladder perforation. [378] The use of the ambiguous language "exceptionally low" rather than providing the material facts provides a reassurance to surgeons whom are not trained in cystoscopy. This ambiguous statement of the Monograph teaches away from safety. In addition, it represents a marketing narrative to large number of gynecologists not able to performing cystoscopy.
- "Rarely are there cases where more mesh needs to be removed for reasons of exposure". This statement demonstrates a blatant disregard of the truth. Almost all of the larger retrospective and prospective studies had demonstrated that mesh exposures (extrusions) rarely resolve without excision. By way of example, Ethicon's 3-year prospective data demonstrated

---

[377] • Verdeja, Ana M., Thomas E. Elkins, Alex Odoi, R. Gasser, and Carlos Lamoutte. "Transvaginal Sacrospinous Colpopexy: Anatomic Landmarks to Be Aware of to Minimize Complications." American Journal of Obstetrics and Gynecology 173.5 (1995): 1468-469

[378] ETH.MESH.07724613

that mesh extrusion persisted in 71% of patients not undergoing surgical excision.[379] The blatantly inaccurate statement herein suggests that PROLIFT is uniquely superior to other meshes, misrepresents the material facts, and represents a marketing narrative.

- "While preexisting dyspareunia due to POP resolves following surgery in the majority of cases, there are cases of new onset dyspareunia following GYNECARE PROLIFT System. In reviewing the early data, it may be as high as 6.9%. lt may resolve with time or local treatment and intervention is required in only a small fraction of patients". This is a misrepresentation of the material facts. Some of the earliest data on PROLIFT and dyspareunia, Milani et al (2005) found a 12.5% rate of de novo dyspareunia (63% with PROLIFT posterior).[380] Published reports from Ethicon's TVM investigators had demonstrated a 13-15.4% incidence of de novo dyspareunia.[381] Additionally, the statement that "intervention is required in only a small fraction of patients" is neither supported by the medical literature or my clinical experience. The majority of untreated patients will not significantly improve. Surgery is often not effective.[382]

From the foregoing as well as my knowledge, training, and experience, as a surgeon, as CEO and COO of medical device companies, and as a labeling consultant to medical device companies, it is my opinion to a reasonable degree of medical and corporate certainty that GYNECARE PROLIFT SURGEON'S RESOURCE MONOGRAPH label was inadequate by medical industry standards, standards known to Ethicon and expected by surgeons.

EXPERT OPINION: The PROLIFT PATIENT LABEL[383] (brochure) WAS INADEQUATE[384]

---

379 Cosson M, Rosenthal C, Debodinance P, Clave H, Berrocal J, Jacquetin B. Prospective clinical assessment of the Total TransVaginal Mesh (TVM) technique for treatment of Pelvic Organ Prolapse - 3 year results. Int Urogynecol J (2008) 19 (Suppl 1):S106. 13 women suffered mesh extrusion. A total of six had undergone excision (5 at one year and one now). If we allow that excisions resulted in cure, 5 of the 7 patients not excised of their extrusion (71%) are with persistent mesh extrusion. Of course it is possible that excisions failed and the 46% overall persistent extrusion rate represents a combination of excisional failures and medical failures. 85 women available at 3 year follow-up

380 Milani et al. Functional and anatomical outcome of anterior and posterior vaginal prolapse repair with prolene mesh. BJOG: an International Journal of Obstetrics and Gynaecology. January 2005, Vol. 112, pp. 107–111.

381 Fatton B, Amblard J, Debodinance P, Cosson M, Jacquetin B. Transvaginal repair of genital prolapse: preliminary results of a new tension-free vaginal mesh (ProliftTM technique) - a case series multicentric study. Int Urogynecol J 2007; 18: 743-752.

Cosson M, Rosenthal C, Debodinance P, Clave H, Berrocal J, Jacquetin B. Prospective clinical assessment of the Total TransVaginal Mesh (TVM) technique for treatment of Pelvic Organ Prolapse - 3 year results. Int Urogynecol J (2008) 19 (Suppl 1):S106
61 women were sexually active prior to TVM. 40 were sexually active at 1 year after implant. 39 are sexually active at 3 years.

382 Crosby, Erin C., Melinda Abernethy, Mitchell B. Berger, John O. Delancey, Dee E. Fenner, and Daniel M. Morgan. "Symptom Resolution After Operative Management of Complications From Transvaginal Mesh." .Obstetrics & Gynecology. 123.1 (2014): 134-39.

383 ETH.01786

384 Patient marketing piece, ETH.00264 bares similar inadequacies and is noted referenced below.

Conventional medical industry standards dictate that patient brochures provide the patient with the material facts necessary for a patient to make an educated decision with regard to a device and or procedure. These requisite material facts include the risks, benefits, alternatives, and uncertainties. Manufacturers are typically aware that surgeons utilize patient labels as part of the patient education and consenting process and routinely provide such labels to physicians for use in their office. In addition, some manufacturers provide brochures directly to the patient, for this same purpose, educating and consenting. This appears to be the case with Ethicon who created an additional label instructing patients to bring the PROLIFT brochure with them to the doctor's office.[385] Standard industry practice dictates the use of accurate, honest, factual, and non-misleading language in these patient labels.

- In its narrative on alternative treatments, it offers Pessary as one of two non-surgical options. It states "Pessary; A device that is inserted in the vagina to help support the pelvic area may help relieve mild symptoms". This statement fails to disclose the important material fact that the pessary also treats moderate to severe symptoms. This omission misleads a patient with moderate or severe symptoms to believe that he or she is not a candidate for this conservative treatment option and thereby encourages surgery with PROLIFT. This paragraph continues and states, "If she is unable to care for the pessary herself, she'll need to see a health care provider for regular check-ups and cleaning of the pessary". Although this is true, it paint an inappropriately burdensome picture. A more appropriate and less ambiguous statement (that would not discourage pessary use) is "Some women may not be able to care for their pessary. In such instances, cleaning will be performed quarterly (or every three months) by a health care professional. The narrative on this important non-surgical alternative to PROLIFT is misleading and does not provide a patient with the material facts requisite to an informed decision.
- "What is GYNECARE PROLIFT. A revolutionary surgical procedure using GYNECARE PROLIFT employs a specially designed supportive soft mesh placed in the pelvis to restore pelvic support. GYNECARE PROLIFT mesh is designed for placement utilizing a technique performed through very small incisions inside the vagina".[386] The common understanding of the adjective "revolutionary" in medicine is, as provided by Merriam Webster, causing or relating to a great change".[387] Ethicon hence states the PROLIFT procedure with its soft mesh placed through very small incisions in the vagina is a great change. Yet, as demonstrated in both literature and my clinical practice, the mesh is anything but soft in vivo. Additionally, I have yet to meet a single surgeon that would characterize the incisions as "very small". Lastly, the brochure conveniently fails to disclose that a minimum of 4 and up to 6 additional incisions is required outside the vagina. The brochure herein uses ambiguous langue that hides material facts, does not disclose material facts,

[385] ETH.00264

[386] The statement of "very small incisions in the vagina" also appears in the patient advertisement piece, ETH.00264

[387] http://www.merriam-webster.com/dictionary/revolutionary

and, and misleads the patient. The patient is thereby prevented from my an informed decision.

- "It can be completed in less than half the time of traditional surgery. Patients experience less pain, quicker recovery, and go home the next day. This statement appeared in both the patient brochure and a separate patient advertisement (label).[388] Although it is possible that a small number of surgeons might be able to perform PROLIFT in less than half the time of traditional surgery, this is not reflected by the literature, some of which that shows that PROLIFT significantly takes longer to perform.[389] Maher et al was able to perform a total PROLIFT significantly quicker then a laparoscopic sacrocolpopexy. However, some of the worlds most experienced surgeons took twice as long to perform the TVM surgery.[390] Furthermore, Maher et al found that PROLIFT was associated with a longer hospital stay and a longer recovery. The claims of superiority reported herein by Ethicon are misleading and do not disclose the material facts. These statements prevent the patient from making an informed decision.
- "It allows for the restoration of sexual function by restoring normal vaginal anatomy". This statement also appears in a patient advertisement (label).[391] Not only is there no data to support this statement, the converse is true. As discussed at length through this report, the PROLIFT mesh contracts and becomes inelastic. It is associated with a remarkable rate of untreated compartment failure. It is associated with over a 40% rate of cessation of sexual activity. The inventor of its method reported a rate of de-novo dyspareunia at least five times greater than native tissue surgery. Ethicon's French TVM study demonstrated moderate to severe vaginal contraction in 12.6% of women. The statement "It allows for the restoration of sexual function by restoring normal vaginal anatomy" is a blatant misrepresentation of the material facts that misleads patients. This statement prevents patients from making an informed decision.
- "Using this new surgical procedure there is often no need to perform a hysterectomy if the uterus itself is not diseased". There is insufficient longitudinal data to support this claim. Ethicon herein does not disclose that there is no substantial level-one evidence to support this claim. Furthermore, this statement may be interpreted to mean that a hysterectomy is typically required with prolapse surgery, therein creating the thought "Hey, if get a PROLIFT, I probably will not need to have a hysterectomy". This statement

---

388 ETH.00264

389 Withagen, Mariëlla I., Alfredo L. Milani, Jan Den Boon, Harry A. Vervest, and Mark E. Vierhout. "Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse." Obstetrics & Gynecology. 117.2, Part 1 (2011): 242-50. Withagen reported native tissue surgery at 45min and PROLIFT at 53.5 min.

390 It is important to note that the most experienced TVM surgeons in the world, the Ethicon's French TVM investigators, reported a mean TVM operative time of 95.1 minutes. Although Maher et al reported a Laparoscopic Sacrocolpopexy time of 97 minutes; this is not meaningfully different then the 95 minute TVM time of the French TVM surgeons. The average length of stay following TVM in the French study was 4.7 days.

391 ETH.00264

claim herein made by Ethicon is a barrier to a patient's ability to make an informed decision.

- "There is also a small risk of the mesh material becoming exposed into the vaginal canal". Ethicon's 1-year TVM data demonstrated a 10-14% rate of mesh exposure and its final 5-year U.S. TVM data would demonstrate a 24% rate of mesh exposure. Clearly the risk of mesh exposure was not small. This was an inaccurate and misleading representation of the material facts. This information prevented patients from making an informed decision.
- "Pelvic floor repair procedures with GYNECARE PROLIFT are appropriate for most patients, even those who have undergone previous operations for pelvic organ prolapse or stress urinary incontinence" (A separate patient advertisement bares a similar statement[392]). This statement is both unsubstantiated by the medical literature and in contradiction to Ethicon's internal documents. Ethicon's French TVM study was limited to patients with advanced POP. As noted elsewhere by way of internal documents, Ethicon stated, "For those cases where an adequate surgical repair is not possible without additional supporting or bridging material, the risks associated with mesh implants have been deemed to be appropriate given the benefit they provide". Ethicon herein indicates its belief that PROLIFT devices are not appropriate for most patients, but rather are indicated for the treatment of a unique subset of patients. This is in line with the subsequent reconditions of the American Board of Obstetricians and Gynecologists and the American Urogynecology association that stipulated that transvaginal mesh surgery could be considered in the treatment of a unique, high risk, patient population if performed by uniquely skilled and trained surgeons. This statement provided in the brochure is a misleading representation of the material facts that prevents a patient from making and informed decision.

From the foregoing as well as my knowledge, training, and experience, as a surgeon, as CEO and COO of medical device companies, and as a labeling consultant to medical device companies, it is my opinion to a reasonable degree of medical and corporate certainty that PROLIFT Patient Brochure was inadequate by medical industry standards, standards known to Ethicon and expected by surgeons.

EXPERT OPINION: THE PROLIFT TRAINING WAS INADEQUATE

The method of implantation trained by Ethicon involves surgical anatomy poorly understood by most urologists and gynecologists. This is a very unique situation. Most devices marketed to surgeons represent improvements on existing instruments and methods. Hence, surgeons are not asked to venture outside of

[392] ETH.00264

their residency or fellowship training, training that was delivered over 4 to 8 years with continued supervision. Ethicon's marketing of PROLIFT represented marketing of novel tools for a novel method. Training was typically offered in a one-day course without any validation of competency. Even more concerning is the fact that surgeons received no training in explantation. Worsening this void is the fact that these surgeons had little or no residency or fellowship training in dissection of the obturator, adductor, and ischiorectal spaces. Hence, they had and have no experience or training upon which they could improvise and attempt extraction of the PROLIFT mesh arms. Blind explanation of mesh that often lies within millimeters of major nerves and blood vessels is a treacherous endeavor for even an expert surgeon trained in the anatomy. Whereas the obturator, pudendal and rectal nerves and blood vessels may lie only a few millimeters from the PROLIFT mesh arms, the most common scissor used in pelvic floor surgery, the metzenbaum scissor, has tips that open greater than 2 cm. The potentially grave consequences of surgical dissection of these spaces by gynecologist and urologists are evident.

Whereas Ethicon trained general gynecologists in one day courses, this training was not sufficient for experts. Dr. Joyce Loman, and Ethicon PROLFIT with extensive PROLIFT experience reported that it took an entire year of fellowship before she became comfortable with the anatomy and dissection required for PROLIFT.[393] Internal documentation demonstrates that approximating the time of PROLIFT introduction to the market, Ethicon recognized that 18% of experts trained by way of cadaver needed to be retrained.[394] Ethicon neither ceased to train by cadaver nor implemented a means of validating the efficacy of such training with follow-up post-training competency testing.

Although Ethicon considered it's a surgeon ready to be a PROLFIT preceptor (and train other surgeons) after as few as 3-5 PROLIFT cases, it experts and trainees did not agree.[395] Ethicon's U.S. TVM investigator, Key Opinion Leader, and perhaps their most experienced and highly compensated U.S. preceptor reported ten cases were hardly enough to expertise in the procedure.[396] Internal documents indicate that 40% of surgeons believed that 20 or more PROLIFT cases were needed to get past the learning curve.[397] Yet, no such minimums were required of preceptors.

Paul Parisi, Ethicon's World Wide Director of Professional Education (2005-2013) testified that he agreed that PROLFIT should have been limited to a highly skilled group of

---

393 Expert report of Joye K. Lowman, M.D., MPH, the case of Patricia L. Hammons, Plaintiff, v. Ethicon, Inc., et al., Defendents. Philadelphia County Court. May Term 2013. No. 3913

394 ETH.62214

395 ETH.MESH.02282833-02282834, Iglesia CB et al. Vaginal mesh for prolapse: a randomized controlled trial. Obstet Gynecol 2010; 116: 1456., ETH.59498

396 Iglesia CB et al. Vaginal mesh for prolapse: a randomized controlled trial. Obstet Gynecol 2010; 116: 1456.

397 ETH.59496-59497

surgeons who could use the product safely and effectively and that the PROLIFT procedure was complex and should only be performed by highly skilled and high volume, very experienced specialists.[398] Yet, in direct contradiction to the testimony of Ethicon's Director of Professional Education, Ethicon's World Wide Medical Director, in his deposition agreed that the pool of highly skilled surgeons was limited and, hence, Ethicon intended to market to lesser skilled surgeons.[399] The 2008 Ethicon Business Plan per the testimony of Ethicon's Product Director, Scott Jones, validated this shift to the training of lesser skilled surgeons, secondary to the limited pool of highly skilled surgeons.[400]

Q. The PROLIFT® in its initial launch and in its development was intended to be used by the top tier surgeons, the most highly skilled surgeons. Correct?

A. Absolutely.

Q. But certainly the business plan for 2008 for the pelvic floor products included taking steps to train the tier 2 surgeons (surgeons not in the top ten percent) on pelvic floor surgery so they could then be brought into the market as well. Correct?

A. I would make that assumption, yeah.

In 2008 Ethicon commissioned a physician survey by Qualitative Research and Consulting. The findings of this survey provide direct validation of the inadequacies of PROLIFT training.[401] "These doctors said things like the following about PROLIFT training:"

"The training is adequate but only for properly selected surgeons with sufficient volume, enough experience and thorough knowledge of pelvic anatomy."

"For those not doing a lot of pelvic surgery, the training may not be adequate. A cadaver lab is not enough. You must scrub in and be proctored on at least 4 or 5 eases."

"The training they provide is appropriate but the problem is they are not requiring surgeons to do all of it. They need to require the review of the CD-ROMS before attending preceptorship Ethicon has the means to do this but they aren't."

"They should not be training everybody. Some surgeons don't have the skill. Training should be a didactic course, then cadaver lab, then proctored for 4 or 5 patients. No certification only for a cadaver course. They should change that."

"They are recruiting doctors who have no business doing it.
They don't have the skill or the clinical volume. We proctors are very frustrated by this. We see people who have no business being there."

---

398 See depositon of Paul Parisi. 766:15-789:25

399 See depositon of David Robinson. 376:14-24

400 See deposition of Scott Jones pg 718, 729,731-734

401 ETH.59475-59508

"The training isn't adequate. I had one lecture and saw a preceptor do a few. I'm not convinced doing 2 to 3 cases with a proctor is adequate training."

"A cadaver lab and seeing 1 or 2 cases probably is not adequate. They could get bad outcomes."

From the foregoing as well as my knowledge, training, and experience, as a surgeon, as preceptor who has trained over 1000 surgeons for medical device companies, and as CEO and COO of medical device companies, it is my opinion to a reasonable degree of medical and corporate certainty that PROLIFT training was inadequate.

Dated: 01/31/2016

Ralph Zipper, M.D. , FACOG FPMRS